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# EPIDEMIOLOGY

Concepts and Methods

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## CHAPTER SIX

# Comparing Measures of Occurrence in Epidemiology

*This chapter describes basic procedures for rate adjustment, commonly used measures of association in epidemiology, and the fundamentals underlying statistical significance testing.*

### Learning Objectives

- Compare and contrast crude, specific, and adjusted rates.
- Explain the rationale for rate adjustment or standardization.
- Perform and interpret the results of age adjustment using both the direct and indirect methods.
- Calculate and interpret each of the following measures of association: risk ratio (cumulative incidence ratio), rate ratio (incidence density ratio), odds ratio, prevalence ratio, percent relative effect, risk difference (cumulative incidence difference), rate difference (incidence density difference), prevalence difference, population rate difference, attributable fraction among the exposed, and population attributable fraction.
- Explain the usefulness of measures of association based on relative and absolute comparisons, respectively.
- Describe the process and rationale for hypothesis testing and determining the statistical significance of an association.
- Define 2000 U.S. standard million population and 2000 U.S. standard population; *a posteriori* comparison; absolute risk; alpha level; clinical (or practical) significance; defined population; directional and non-directional hypothesis; disease odds ratio; excess risk, rate, and prevalence; indirectly standardized rate; population risk difference and population prevalence difference; p-value; referent; relative odds; and relative risk.

of the association. Furthermore, it can tell us whether or not an apparent association is statistically significant, although this is not a reason it is preferred over statistical significance testing. If a confidence interval for a ratio measure of association contains 1.0, then the association is not statistically significant. If for a difference measure of association it contains 0.0, then it is not statistically significant. In short, a confidence interval for a measure of association can be used to get an idea of the probable magnitude and range of the association in the sampled population. If desired, it can also be used to determine whether or not the association is statistically significant, although those who dislike statistical significance testing will not see this as an advantage.

The use of confidence intervals over significance testing has gained many proponents in epidemiology, and confidence intervals are increasingly the preferred way of reporting results in many epidemiologic, public health, and biomedical journals. Nevertheless, statistical testing is still used and has its adherents. Therefore, it is prudent to be familiar with both methods. More is said about significance testing and confidence intervals in chapter 8 and succeeding chapters.\*

## SUMMARY

- Crude rates are overall, summary measures of occurrence for defined populations. Specific rates are measures of occurrence for distinct subgroups within a defined population, such as age-specific or sex-specific rates. Crude rates are more convenient to compare between populations than specific rates, especially if there are many specific rates to compare. Unlike specific rates, however, crude rates can be distorted (confounded) by differences in the underlying distributions of the populations being compared, particularly age distributions.
- Adjusted rates, like crude rates, are also overall measures of occurrence, but they have been statistically modified (adjusted) to remove the potential distorting effects of one or more factors like age, sex, or race/ethnicity differences between the populations being compared. Adjusted rates permit fair, unbiased comparisons between overall rates.
- There are two basic methods of rate adjustment—the direct and indirect methods. The direct method uses the specific rates in the populations being compared to develop adjusted rates based on a standard population. The indirect method applies the specific rates in the reference population to the study population to develop a standardized mortality (or morbidity) ratio.

\*Generally speaking, modern theory in epidemiology holds that study populations do not need to be considered representative samples of some larger general population to provide valid and reliable findings, except in the case of certain cross-sectional studies. This conception, however, can make it difficult to explain the application of confidence intervals and significance testing, which are firmly based on sampling theory. Tools like confidence intervals or tests of significance are used in most epidemiologic studies as relative indicators of the reliability of the findings even if in a technical sense the assumption of random sampling from a normal population is not met.

## CHAPTER SEVEN

# Association and Causation in Epidemiology

*This chapter discusses differences among spurious, noncausal, and causal associations, the various types of causes, and common guidelines used in assessing causation in epidemiologic studies.*

### Learning Objectives

- Describe and give examples of spurious, noncausal, and causal associations in epidemiology.
- State the common reasons for spurious and noncausal associations, respectively.
- Distinguish among necessary, sufficient, necessary and sufficient, necessary but not sufficient, not necessary but sufficient, and not necessary and not sufficient causes and give examples of each type.
- Describe and give examples of direct and indirect causal associations.
- Briefly describe the causal pie model.
- Discuss six guidelines based on Hill's postulates for judging potential causal associations, including the advantages and limitations of each criterion, respectively.
- Explain the importance of finding causal associations in epidemiology.
- Define predisposing or enabling factors, statistical association, and threshold.

### INTRODUCTION

As indicated in chapter 1, one of the primary goals of epidemiology is to discover the *causes*\* of morbidity and mortality in human populations. This goal has immense practical significance for health professionals because a better

\*There are many terms relating to or derived from the root term *cause*. These include causation, causality, causal, causative, cause-effect, etiology, and so forth. These terms are not defined separately in this chapter, but each refers to something similar.

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understanding of the causes of morbidity and mortality often leads to more effective prevention, treatment, and control measures and consequently to a reduction in disease incidence, prevalence, or severity.

A *statistical association* between a given exposure and outcome is the starting point for consideration of a causal relationship in epidemiology. A *statistical association* implies that the exposure is related to a change in the *probability* of the outcome. It does not automatically mean that the exposure *causes* the outcome.<sup>1</sup> Hence, a frequently cited maxim in introductory statistics courses is: “Association does not necessarily imply causation.” In short, statistical associations should not be accepted at face value. They should be examined for alternate explanations before any conclusions are drawn. Even a statistically significant association (chapter 6) does not guarantee that a true association exists, much less that the association is causal. A *causal association* between an exposure and outcome means that a change in the frequency of the exposure in a population *will result* in a change in the frequency of the outcome, even though not every individual with the exposure will change. A statistical association only implies that those with the exposure are more or less likely to develop the outcome.

To summarize briefly, a valid statistical association means it is *more or less likely* that the outcome will occur in the presence of the exposure, while a valid causal association means that changes in the frequency of exposure will result in changes in the frequency of the outcome. It should be noted that a causal association may be positive (the exposure increases the outcome) or negative (the exposure decreases the outcome). In the former case, the exposure is *hazardous*; in the latter case it is *protective*. The remainder of this chapter focuses on examining statistical associations to determine whether or not they are likely to represent causal associations. Many factors must be considered, and any conclusions must be based on an overall assessment of the evidence.

### TYPES OF ASSOCIATION

Statistical associations found in epidemiologic studies (e.g., OR = 3.4) can be categorized into three types. These categories are mutually exclusive.

- Spurious associations
- Noncausal associations
- Causal associations

#### Spurious Associations

**Spurious associations** are literally *false* associations. Though they may be found in a particular study population, they are probably due to other explanations. Spurious associations usually result from *random error* (chance) or *bias*, which are discussed more fully in chapter 8. For example, as mentioned in chapter 6, an association is generally considered statistically significant if  $p \leq 0.05$ . This implies that, assuming there is no association, chance is an

unlikely explanation for the finding given the sample size and strength of the association. Nonetheless, we would still predict that as many as five times out of 100 the association could be due to chance alone. Thus, even statistically significant associations that result from well-executed epidemiologic studies can sometimes be spurious. Inderjit S. Thind, for instance, conducted an ecological study of the association between dietary intake and cancer using a sample of 60 countries. He found a number of significant statistical associations, including some that were biologically implausible and which he thought to be spurious. In his discussion of the findings, he reiterated a common concern in broad-based studies where large numbers of statistical tests of significance are performed. Specifically, he cautioned the readers by stating, "The . . . large numbers of correlations . . . with [some] significant associations occurring purely by chance, suggest extreme care in assessing the role of specific dietary items as risk factors and using the results as the basis for public policy."<sup>2(p162)</sup>

Spurious associations may also arise from sources of bias. *Bias*, which is discussed in chapter 8, is a type of systematic (nonrandom) error in the design, conduct, or analysis of epidemiologic studies, such as the use of flawed measurement techniques, differential recall among study and comparison groups, or selection of study and comparison groups that are dissimilar. Bias can be quite insidious. Consider a hypothetical case-control study of the relationship between exposure to low-frequency electromagnetic fields, such as those generated by electric power lines, electric blankets, and electric alarm clocks, and the incidence of childhood leukemia. The cases consist of patients from area hospitals newly diagnosed with childhood leukemia, and the controls are those without leukemia of similar age, sex, and racial/ethnic background who have been randomly selected from the communities served by the hospitals. The parents of cases and controls are then queried about their children's exposure to low-frequency electromagnetic fields. The parents of the cases may be more likely to recall their children's exposures than those of the controls since they are probably more motivated to remember past exposures that might help explain their children's leukemia than are the parents of the controls. If this is true, the study could result in a *spurious* association between exposure to low-frequency electromagnetic fields and the incidence of childhood leukemia.

### Noncausal Associations

**Noncausal associations** are real associations, but they are *not* causal associations. That is, a change in the frequency of the exposure in a population does not necessarily result in a change in the frequency of the outcome. Noncausal associations often result from *confounding*, which is discussed in chapter 8. The association exists because the exposure is associated with another factor that in turn is associated with the outcome. A whimsical example is provided by Max Michael III, W. Thomas Boyce, and Allen J. Wilcox.<sup>3</sup> Dr. Al Betze-rov conducted a prospective cohort study to test his hypothesis that gambling

causes cancer. He chose two neighboring states, one where gambling was legal and the other where it was not. He then followed randomly selected samples of subjects from each state matched by age, sex, urban/rural differences, and family income for 10 years. At the conclusion of the study, he noted a statistically significant positive association between gambling and cancer. Specifically, the residents of Nevada had a higher rate of cancer than those from Utah. The association, although real, was *not* one of cause-effect. Unfortunately for Dr. Betzerov, one of the states he chose was Utah. Utah is a state composed of a large number of Mormons, who have very different lifestyles from typical Nevada residents, who are not Mormons. The fact that the Mormon Church requires its adherents to abstain from tobacco and alcohol explains this association. The apparent causal association between gambling and cancer was due to confounding by alcohol and tobacco use, which are higher in Nevada than in Utah. In other words, alcohol and tobacco use are associated with gambling and are directly linked to cancer. Therefore, although gambling itself does not cause cancer, its association with causes of cancer produces a noncausal association with cancer. This type of association has also been referred to by some as a "spurious association" in that it can lead to an erroneous conclusion about cause and effect.

Risk markers, which were referred to in chapter 1, represent noncausal associations. Although these associations result from confounding with actual risk factors, they are still real associations that have practical significance in screening for disease.<sup>4</sup> For example, calcification in the coronary arteries is a risk marker for coronary heart disease. It does not cause the disease, but it is associated with an increased risk of its occurrence. Its role in coronary heart disease is therefore properly classified as noncausal. Nevertheless, screening for coronary calcium has become an increasingly popular, though controversial, method of detecting possible presymptomatic heart disease (see chapter 13).

Noncausal associations can also result when the defined exposure is a consequence of the outcome instead of the other way around. Hypertension, for example, may result from kidney disease. Thus, one may find a statistical association between hypertension and kidney disease, but in this example, hypertension could not be considered a cause of kidney disease because the exposure does not *precede* the outcome and therefore cannot alter its frequency. In this example, kidney disease is a cause of hypertension. This type of hypertension is generally referred to as secondary hypertension to differentiate it from primary hypertension, which can cause kidney disease.

### Causal Associations

**Causal associations** are those in which changes in the frequency of the exposure in a population produce a change in the frequency of the outcome. In epidemiology, we cannot prove causal associations because it is impossible to account for all the other factors that might play some role in an association, especially in observational studies where there may be many unrecognized,

and therefore uncontrolled, variables. Well-designed experimental epidemiologic studies can come much closer to establishing causation than observational studies, but even in these studies there may be other influential factors of which the investigator is unaware. Since no two human beings are exactly alike in their makeup or reactions to external stimuli, one cannot always be assured that even randomized groups of people are perfectly comparable. Even laboratory experiments with mice rely on well-defined strains to minimize intraspecies differences that can invalidate the results of an experiment.

A given association may not be conclusively spurious, noncausal, or causal. This is because random error can never be completely eliminated as a possible reason for an association in an epidemiologic study, although it can be greatly minimized. Similarly, it would be extremely difficult to discount any possibility of bias in a study. The same can be said for possible confounding. Thus, the job of the epidemiologist is to determine which type of association is more likely, and this is not always an easy task.

Since our main concern is identifying causal relationships when they exist, we need some guidance in determining whether an association is likely or not to be a causal one. In practice, the determination of a causal association is based on a careful review and judgment of all relevant information available, and never on the basis of one or two studies alone, especially observational studies. It is somewhat like trying a criminal case where there are no eyewitnesses to the crime. The prosecutor has to rely on circumstantial evidence to convince a jury beyond a reasonable doubt that the defendant is guilty. It was based on a thorough review of major epidemiologic and non-epidemiologic studies that in 1964 the Surgeon General of the U.S. Public Health Service first concluded that cigarette smoking is a cause of lung cancer.<sup>5</sup> Before discussing some of the guidelines used to assess potential causal associations, it should be worthwhile to first examine the concept of causation in more detail. This is the subject of the following section.

## TYPES OF CAUSES

With communicable diseases the concept of causation appears to be relatively straightforward. However, as discussed in chapter 3, this apparent simplicity can be deceiving. Not everyone exposed to *Mycobacterium tuberculosis* (the bacterium implicated in tuberculosis), for example, develops tuberculosis. A number of host and environmental factors must also be considered. Similarly, not everyone exposed to cold germs gets a cold. In fact, the more we learn about causation, the more complex it seems. With many noncommunicable diseases, especially chronic conditions like arthritis, mental illness, Alzheimer's disease, multiple sclerosis, cardiovascular disease, diabetes, and so forth, the causal pathways can be extremely complex. Multifactorial etiology (chapter 2) is the rule rather than the exception for most contemporary health-related problems.

**Necessary and Sufficient Causes**

To get a better understanding of causation as it is commonly used in epidemiology it is helpful to look at different types of causes.\* A **necessary cause** is an exposure that is *required* for a particular outcome to occur. Therefore, it is always associated with the outcome. If the exposure is absent, the outcome cannot occur. A **sufficient cause** is an exposure that by itself will produce a particular outcome, but it may not be the only cause of the outcome. Consequently, the outcome may occur without the exposure if the outcome is also caused by other exposures. These two classifications of causes give rise to four possible combinations,<sup>6</sup> which are shown below in the following 2 × 2 table.

		<b>Necessary</b>	
		Yes	No
<b>Sufficient</b>	Yes	A	C
	No	B	D

*Combination A* represents a **necessary and sufficient cause**. This is a cause that is required to produce a particular outcome *and* which is able to cause the outcome by itself. This can be represented by:

$$\text{Exposure X} \rightarrow \text{Outcome Y}$$

where Exposure X is the specified cause, and Outcome Y is the specified outcome.

Necessary and sufficient causes are not very common in the real world. One example of a condition that results from a necessary and sufficient cause is lead poisoning. Exposure to lead is *necessary* to produce lead poisoning, and it is also *sufficient*. The rabies virus might also be considered a necessary and sufficient cause of human rabies. It is *not* essential that a necessary and sufficient cause always produces the outcome. Observations have shown, for example, that not everyone presumably infected with the rabies virus contracts the disease even if they have not been immunized.<sup>7</sup> Nevertheless, anyone who contracts rabies must have the virus (i.e., it is necessary), and no other known cause must be present for the disease to occur (i.e., it is sufficient). It is important to emphasize, however, that as knowledge of disease causation expands, classifications may need to be revised. We may learn in the future, for example,

\*The types of causes discussed here and subsequently are assumed to be hazardous rather than protective so as to simplify the discussion.

that some causes thought to be necessary and sufficient would be better classified in another way. At one time many believed that cancer was caused by a single factor, still undiscovered. Today we recognize its multifactorial etiology.

*Combination B* in the above table represents a **necessary but not sufficient cause**. This is a cause that is required to produce a specified outcome *but* is *not* able to cause the outcome by itself. Other causes are necessary for the outcome to occur. This can be represented by:

$$\text{Exposure X} + \text{Other Causes} \rightarrow \text{Outcome Y}$$

Alcoholism is a disease in which alcohol consumption is a necessary but not sufficient cause of the disease. Alcohol consumption is definitely necessary for alcoholism to develop, but other factors, including genetic, social, behavioral, and environmental factors, also appear to be necessary for the disease to manifest itself.

*Combination C* represents a **not necessary but sufficient cause**. This is a cause that is *not* required to produce a specified outcome *but* when present is able to cause the outcome by itself. This means that there are other causes of the outcome. A not necessary but sufficient cause may be represented by:

$$\text{Exposure X} \rightarrow \text{Outcome Y} \text{ and } \text{Exposure Z} \rightarrow \text{Outcome Y}$$

where Exposure Z is some other independent cause of Outcome Y. Ionizing radiation at high doses will cause sterility in men. Heavy exposure to certain pesticides will do the same. In this example, Exposure X is ionizing radiation, Exposure Z is a specific pesticide, and Outcome Y is sterility in men. Thus, sterility in men has more than one cause. Both ionizing radiation and certain pesticides are capable of causing sterility in men (at high doses).

*Combination D* denotes a **not necessary and not sufficient cause**. This is a cause that is *not* required to produce the specified outcome *and* when present is *not* able to cause the outcome by itself. Hence, there are other causes of the specified outcome. A not necessary and not sufficient cause is known as a **contributory cause**. It can be represented by:

$$\text{Exposure X} + \text{Other Causes} \rightarrow \text{Outcome Y} \text{ and } \text{Exposure Z} \rightarrow \text{Outcome Y}$$

where Exposure Z is another independent cause of Outcome Y. Not necessary and not sufficient causes are very common causes of chronic diseases. For example, a sedentary lifestyle is not necessary and not sufficient to cause coronary heart disease (CHD). It is not required for CHD development, nor is it considered sufficient to cause CHD by itself. It is, however, a contributory cause of CHD, and when present with certain other contributory causes, such as high blood cholesterol, family history of heart disease, hypertension, cigarette smoking, and so forth, can lead to the development of CHD. That is, the frequency of CHD will be higher in groups with these factors than in groups without them.

A logical extension of this paradigm is one conceptualized by Kenneth J. Rothman and referred to as the **causal pie model**.<sup>8</sup> One can imagine one or

more intact pies neatly divided into several pieces symbolizing what Rothman calls **component causes**. Each pie represents a *sufficient cause* of a particular disease, and each component cause has an essential part in causing that disease. There may be several sufficient causes (pies) made up of various combinations of some of the same and different component causes for any given disease. Whatever the combination, the component causes work together to cause the disease.<sup>8</sup> The causal pie model may remind one of the information asked for on a death certificate regarding the causes of death (see exhibit 2-1 in chapter 2). In a sense, the immediate, antecedent, and underlying causes of death, as well as other significant conditions, seem to parallel the component causes for a particular death.

As intimated earlier, in epidemiology causation is determined by what occurs in populations or groups of people as opposed to what occurs in any particular individual. We know, for example, based on the Framingham Heart Study that people who live certain lifestyles die more frequently from coronary heart disease than those with healthier lifestyles. From the group data, we can make predictions about individuals based on their lifestyle habits, but we cannot expect that the predictions will always be correct. Everyone seems to know someone, for example, who smoked four packs of cigarettes a day, had high blood pressure, and drank like a fish, but lived until 105. Undoubtedly, this person met an “untimely” death when his bungee cord broke after jumping off a bridge. The exception, however, does not make the rule.

#### Direct and Indirect Causes

Causal associations can also be classified as direct or indirect. A **direct causal association** (or **direct cause**) can be thought of as representing a causal pathway in which there are *no* intermediate variables, while an **indirect causal association** (or **indirect cause**) involves one or more intervening factors.<sup>9</sup> For example, in a direct causal association, X causes Y, where X is the causative exposure, and Y is the outcome. In an indirect causal association, I causes X, which in turn causes Y. While I is a direct cause of X, it is an *indirect* cause of Y. Since I causes X, and X causes Y, it follows that I causes Y based on the definition of a causal association. A change in the frequency of I in a population will result in a change in the frequency of X, which in turn will result in a change in the frequency of Y. Thus, I can be considered an indirect cause of Y.

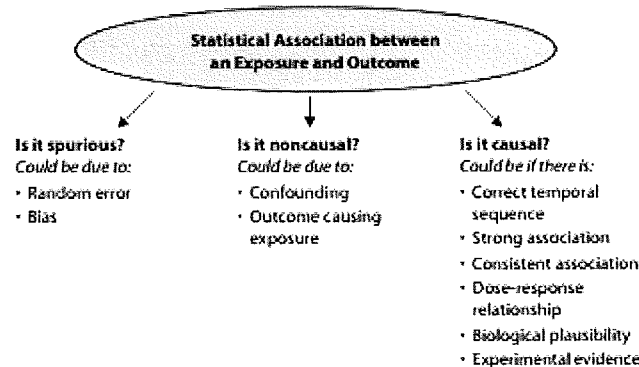
Indirect causes can include a variety of **predisposing or enabling factors** that precede the direct cause. For example, excessive heat applied to the skin is the direct cause of burns, but the exposure to the heat may be influenced by a dangerous working environment or failure to follow certain safety precautions, which might be considered indirect causes of burns. Also, the human immunodeficiency virus (HIV) is said to be the direct cause of AIDS, but factors that facilitate contracting HIV include sharing syringes and promiscuous sexual behaviors. In practice, controlling the predisposing or enabling factors should result in a decrease in frequency of the outcome. Therefore, *predisposing or enabling factors* are often referred to as risk factors.

Whatever classification scheme is used, most contemporary health-related problems appear to have multiple causes. This multifactorial etiology, which has been referred to often in this text, presents a challenge to epidemiologists who are concerned with unraveling the determinants of morbidity and premature mortality and to those whose efforts are directed toward their prevention and control. As our knowledge of the natural history of health problems expands, the models of causation and the methods of intervention will continue to undergo change. An interesting article dealing with different conceptions of causation from an epidemiologic and philosophical perspective is one published in the *Journal of Epidemiology and Community Health* by M. Parascandola and D. L. Weed.<sup>10</sup> While their recommendations may be at odds with many epidemiologists, the discussion itself is can be enlightening, especially for those new to this topic.

### GUIDELINES FOR ASSESSING CAUSATION

As shown in figure 7-1, determining whether a statistical association is causal, involves a number of considerations. One must ask if the observed association is likely to be spurious. Random error or bias could explain an association found in a study population. On the other hand, the association could be a noncausal association. Noncausal associations may be due to confounding by an extraneous factor or because the outcome is responsible for the exposure instead of vice versa. Of course, another option is that the association is causal. Okay, you may say, we know the options, but how can we tell if the association is likely to be a causal one? The first step is to examine whether the alternate explanations are plausible. Specifically, is the associa-

**Figure 7-1 Deciding Whether an Association Is Likely to Be Causal**



tion likely due to random error, bias, confounding, or a reserved causal sequence? This may take some critical thinking, further analysis, or consultation. If these seem to be unlikely explanations, it can be helpful to review some generally accepted guidelines for establishing causation such as those described by Sir Austin Bradford Hill.

In 1965, Sir Austin Bradford Hill, Professor Emeritus of Medical Statistics with the University of London, delivered a landmark address where he outlined nine criteria that could be used to determine if statistical associations were likely to represent causal associations.<sup>31</sup> His reasoning built on the earlier work of others, such as John Stuart Mill, who in 1856 had defined several canons from which causal relationships could be deduced.<sup>6</sup> Over the years many authors have articulated or modified Hill's basic criteria, which have become known as **Hill's postulates**. Using these as a focal point, the following six guidelines should be helpful in deciding whether or not statistical associations are likely to represent causal associations (figure 7-1). In the end, the process of determining causation is largely subjective except for the first guideline, which is actually a requirement.

- **Correct temporal sequence.** In order for an exposure to be considered a cause of an outcome, it must *precede* the outcome. Of all the guidelines used to judge whether an association is causal or not, this is the only one that is considered *absolutely essential*. Exposures that occur concurrently with an outcome or subsequent to an outcome cannot be considered causal because they do not alter the frequency of the outcome. Determining if an exposure precedes an outcome can be problematic in cross-sectional studies where exposure and outcome are assessed concurrently. For example, in a cross-sectional study designed to determine if there is a relationship between the prevalence of excess body weight and osteoarthritis, it may not be clear which factor came first. Thus, the correct temporal sequence cannot be established reliably. This can also be a problem in case-control studies where the prevalence of the outcome is assessed instead of its incidence.
- **Strength of the association.** In general, the stronger an association between a given exposure and outcome (see table 6-3), the more likely the association is causal. When the risk ratio is very high, for example, it is more difficult to explain away the association due to unrecognized or subtle sources of bias or confounding. Compared to nonsmokers, those who smoke and are exposed to high levels of asbestos in their jobs have a fifty- to ninety-fold increased risk of lung cancer. It seems improbable that these factors are not causative. Even if some bias or confounding exists, it is unlikely that it would account for the entire relationship. This is not to say that small associations cannot also be causal in nature. This is one reason why several guidelines are needed to assess causality.
- **Consistency of the association.** When other investigators studying different populations at different times in different places using different methodologies obtain similar findings with regard to a specific association, it

increases the probability that the association is causal. In concluding that cigarette smoking is a cause of lung cancer, the Advisory Committee to the Surgeon General of the United States cited diverse epidemiologic and other studies showing a strong relationship between smoking and lung cancer.<sup>5</sup> One way of determining if an apparent association is likely to be due to random error is to replicate the study. If the findings are consistent, it strengthens the case for a causal association, assuming there are no significant sources of bias or confounding in the studies.

- **Dose-response relationship.** In general, if increased levels of exposure lead to greater frequencies of the outcome, then this is suggestive of a causal relationship. Heavy smokers, for example, have been shown to be at a higher risk of lung cancer than light smokers. In fact, a linear dose-response relationship between smoking and lung cancer can be demonstrated based on the number of cigarettes smoked per day. The absence of a dose-response relationship does not necessarily mean that an association is non-causal, however. A threshold may exist. A **threshold** is a level of exposure (dose) that must be reached before effects become apparent. Below the threshold, there are no observed effects. Copper, which may be found in small quantities in drinking water and certain foods, demonstrates a threshold; that is, copper has no adverse effects until it reaches a certain level in the body. In fact, in very small quantities it is an essential mineral needed for proper growth and development. On the other hand, a dose-response relationship could be due to a strong confounding factor that closely follows an exposure.<sup>12</sup> Once again, several guidelines should be considered in assessing causation.
- **Biological plausibility.** The basic question here is, does the association make biological sense? Is the association credible based on our understanding of the natural history of the disease or possible pathogenic mechanisms? When Thind found significant associations for protein, fat, and caloric intake and certain forms of leukemia, he could offer no biological evidence to support the associations, thereby casting doubt on their authenticity.<sup>2</sup> Failure to make biological sense, however, does not necessarily negate the possibility of a causal association. In some cases, our understanding of the biological mechanisms may be incomplete, and what does not make sense today may make sense sometime in the future. From a contemporary vantage point, it seems difficult to understand why the theory of contagion was considered controversial as an explanation for the spread of epidemics during the Middle Ages.
- **Experimental evidence.** Having experimental evidence to support an association between a given exposure and outcome strengthens the case for a causal association. Well-designed randomized controlled trials, for example, can provide strong corroboration of a suspected causal association. This is because this study design, properly implemented, can virtually eliminate selection bias and confounding as alternate explanations for a causal

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association (see chapters 8 and 12). Of course, the degree of control possible in epidemiologic experiments is not to the same level as that in animal studies. Nevertheless, they can be powerful tools for establishing causation. Evidence from nonepidemiologic experiments can also be used in assessing cause-effect relationships. Because of the limited circumstances in which experimental studies can be conducted with humans, some associations will not be testable in this manner. We would not perform a randomized controlled trial on the effects of microwave radiation on cataract development, for example, because such a study would be unethical even if some were willing to volunteer for the investigation.

Table 7-1 ranks the most common types of epidemiologic studies in descending order of the degree to which identical findings of a statistical association are likely to demonstrate a causal association. The ranking is based on the relative probability of encountering unrecognized bias, confounding, or other errors within the specific study designs. It also assumes that the studies have been planned appropriately and conducted to minimize errors. A poorly designed experimental study can provide less convincing evidence of causality than a well-designed observational study. It should be kept in mind, however, that causality is never determined based on the findings of one study alone. Causation is a judgment based on relevant, cumulative information. Meta-analyses (chapter 12) have provided some hope of reaching more definitive conclusions in epidemiologic studies. Whether they will fulfill this hope depends on the care in which they are designed, implemented, and interpreted.

**Table 7-1 Ranking of Common Epidemiologic Studies in Terms of the Relative Probability that the Findings Represent Causal Associations**

1. Randomized Controlled Trial	5. Case-Control Study
2. Group Randomized Trial	6. Cross-Sectional Study
3. Prospective Cohort Study	7. Ecological Study
4. Retrospective Cohort Study	8. Descriptive Study

### SUMMARY

- Statistical associations found between given exposures and outcomes can be of three types—spurious, noncausal, or causal. Spurious associations are false associations that are usually due to random error or bias. Noncausal associations usually result from confounding, although they can also occur when the exposure is the result of the outcome instead of the other way around. Risk markers represent noncausal associations that have practical value in screening for disease. Causal associations are ones in which a change in the frequency of the exposure results in a change in the frequency of the outcome in a population.

- Causes can be classified as to whether or not they are necessary and/or sufficient and whether they are direct or indirect. A necessary cause is one that is required to produce an outcome, while a sufficient cause is one that can produce the outcome by itself (i.e., in the absence of other known causes). The most common types of causes are those that are not necessary and not sufficient. These are known as contributory causes and are the causes that account for most contemporary health-related problems. The causal pie model expands upon the not necessary and not sufficient causes by considering a constellation of component causes that are sufficient to cause disease. Direct causes do not involve any intermediate factors in the causal pathway. Indirect causes include a variety of predisposing or enabling factors that precede the direct cause of an outcome. Controlling indirect causes can reduce the incidence of particular outcomes and is sometimes easier than controlling the direct causes.
- Because it is not possible to prove causation directly, it is helpful to have reliable guidelines upon which to judge a statistical association in terms of its likelihood of being causal. A final decision regarding causation should be based on all relevant information and not just on the basis of one or two studies, especially observational studies. Six guidelines, derived from Hill's postulates, should help in determining whether an association is likely to be causal. These guidelines are correct temporal sequence, strength of the association, consistency of the association, dose-response relationship, biological plausibility, and experimental evidence. Of these guidelines, only correct temporal sequence is required for an association to be considered causal. The others are highly suggestive of causation, however, especially when all or most of them are met.

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#### New Terms

- |                                  |  |
|----------------------------------|--|
| • biological plausibility        | • indirect cause                         |
| • causal association             | • necessary and sufficient cause         |
| • causal pie model               | • necessary but not sufficient cause     |
| • component causes               | • necessary cause                        |
| • consistency of the association | • noncausal association                  |
| • contributory cause             | • not necessary and not sufficient cause |
| • correct temporal sequence      | • not necessary but sufficient cause     |
| • direct causal association      | • predisposing or enabling factors       |
| • direct cause                   | • spurious association                   |
| • dose-response relationship     | • statistical association                |
| • experimental evidence          | • strength of the association            |
| • Hill's postulates              | • sufficient cause                       |
| • indirect causal association    | • threshold                              |

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### Study Questions and Exercises

1. For each of the following statements indicate whether the results are more likely to be due to a spurious association, a noncausal association, or a causal association. Also, explain the reasons for your answers.
  - a. A case-control study revealed that there was a moderate to strong association between coffee consumption and deaths from coronary heart disease. Other studies have shown that those who drink coffee are more likely to smoke than those who do not drink coffee.
  - b. A prospective cohort study showed that women who exercise regularly were less likely to contract cancer than women who exercised only occasionally or not at all. The exercise group was selected from women attending a fitness center, and the comparison group was selected from women attending a weight-loss clinic.
  - c. A large randomized controlled trial showed that folic acid supplementation by prospective mothers significantly reduced the incidence of neural tube defects in their offspring. This finding was confirmed in subsequent studies.
  - d. A large exploratory epidemiologic study examined the possible relationship of 25 different lifestyle behaviors to teenage suicide. One of the findings was a positive association between bicycle helmet use and suicide ( $p = 0.05$ ) that had not been previously reported in the literature.
2. On bottles of wine and other alcoholic beverages, it states, "According to the Surgeon General, women should not drink alcoholic beverages during pregnancy because of the risk of birth defects." Discuss the evidence that alcohol consumption causes birth defects using the six guidelines for causation discussed in this chapter. For each guideline, describe the degree to which the evidence supports a conclusion of causation and the reasons for your response. In answering this question it may be necessary to consult a review of epidemiologic literature on alcohol consumption and birth defects.
3. Provide an example other than one used in this chapter of a necessary and sufficient cause, a necessary but not sufficient cause, a not necessary but sufficient cause, and a not necessary and not sufficient cause of disease, respectively. Also indicate why your examples are appropriate.
4. Give two examples, respectively, of direct and indirect causes of disease and justify your choices.

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### References

1. Vogt, W. P. (1999). *Dictionary of Statistics and Methodology: A Nontechnical Guide for the Social Sciences*, 2nd ed. Thousand Oaks, CA: Sage Publications.
2. Thind, I. S. (1986). Diet and Cancer—An International Study. *International Journal of Epidemiology* 15(2): 160–162.

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3. Michael, M. III, Boyce, W. T., and Wilson, A. J. (1984). *Biomedical Bestiary: An Epidemiologic Guide to Flaws and Fallacies in the Medical Literature*. Boston: Little, Brown, and Company.
4. Szklo, M., and Nieto, F. J. (2000). *Epidemiology: Beyond the Basics*. Gaithersburg, MD: Aspen Publishers, Inc.
5. U.S. Department of Health, Education, and Welfare (1964). *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service*. USPHS Publication No. 1103. Washington, DC: U.S. Government Printing Office.
6. Last, J. M., ed. (2001). *A Dictionary of Epidemiology*, 4th ed. New York: Oxford University Press.
7. Chin, J., ed. (2000). *Control of Communicable Diseases Manual*, 17th ed. Washington, DC: American Public Health Association.
8. Rothman, K. J. (2002). *Epidemiology: An Introduction*. New York: Oxford University Press.
9. Jekel, J. F., Elmore, J. G., and Katz, D. L. (1996). *Epidemiology, Biostatistics, and Preventive Medicine*. Philadelphia, PA: W. B. Saunders Company.
10. Parascandola, M., and Weed, D. L. (2001). Causation in Epidemiology. *Journal of Epidemiology and Community Health* 55: 905-912.
11. Hill, A. B. (1965). The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine* 58: 295-300.
12. Brownson, R. C., Remington, P. L., and Davis, J. R. (1998). *Chronic Disease Epidemiology and Control*, 2nd ed. Washington, DC: American Public Health Association.

## CHAPTER EIGHT

# Assessing the Accuracy of Epidemiologic Studies

*This chapter deals with the accuracy of epidemiologic studies, specifically validity and precision. In particular, threats to accuracy in the forms of bias, confounding, and random error are examined.*

### Learning Objectives

- Define and explain accuracy, validity, and precision.
- Compare and contrast internal and external validity.
- Distinguish between selection and information bias.
- Identify potential types of selection bias based on study descriptions.
- Identify potential types of information bias based on study descriptions.
- Differentiate between differential and nondifferential misclassification and the potential consequences of each.
- Identify basic methods of controlling selection and information biases, respectively.
- Explain the concept of confounding, the requirements for confounding, and the potential consequences of confounding.
- Identify specific methods to minimize confounding.
- Define random error and its major components.
- Describe the major methods of assessing random error, including their relative strengths and weaknesses.
- Explain two methods of reducing random error in a study.
- Define beta level; error; individual, pair, and frequency matching; interval estimation; systematic and nonsystematic error; positive and negative bias; positive and negative confounding; potential confounder; power; probability sample; residual confounding; Simpson's paradox; source population; and type I and type II errors.

In other words, researchers seeking to understand the causes of homelessness by studying individual risk factors for homelessness are committing a type III error by giving the right answer to the wrong problem.

**The Second Definition**

Another definition of a type III error has to do with statistical significance or hypothesis testing. Basically, it occurs when one rejects the null hypothesis ( $H_0$ ), and the alternate hypothesis ( $H_A$ ) is directional but in the opposite direction of the true association. For example:

$$H_0: OR = 1.0$$

$$H_A: OR > 1.0$$

If one rejects the null hypothesis that the odds ratio equals one in favor of the alternate hypothesis that the odds ratio is greater than one, but in reality the true odds ratio is less than one, then the researcher has committed a type III error. This concept of a type III error is due to sampling variation (i.e., random error). Theoretically, a larger sample should lead to a lower probability of making a type III error. L. Leventhal and C. Huynh (1996) have indicated that this kind of a type III error can also occur when the alternate hypothesis is non-directional as shown below.

$$H_0: OR = 1.0$$

$$H_A: OR \neq 1.0$$

Even though the alternate hypothesis is non-directional, some researchers will assume that the direction of the relationship in their study population is the correct one. If it is not, a type III error has been committed.

References: Kimball, A. W. (1957). Errors of the Third Kind in Statistical Consulting. *Journal of the American Statistical Association* 52 (278): 133-142; Leventhal, L., and Huynh, C. (1996). Directional Decisions for Two-tailed Tests: Power, Error Rates, and Sample Size. *Psychological Methods* 1 (3): 278-292; Schwartz, S., and Carpenter, K. M. (1999). The Right Answer for the Wrong Question: Consequences of Type III Error for Public Health Research. *American Journal of Public Health* 89 (8): 1175-1180.

As implied in chapter 6, statistical significance (hypothesis) testing has a number of limitations and has found disfavor among many epidemiologists. Some common objections are: (a) the cut-off point for determining statistical significance is completely arbitrary; (b) the p-value is confounded by the effects of sample size and strength of the association; and (c) statistical significance is often misinterpreted. With regard to the first point, one can argue convincingly that there is very little difference between  $p = 0.04$  and  $p = 0.06$ . Yet, with an arbitrary cut-off point of  $p = 0.05$ , two different conclusions would be reached based on these similar values. The second point is important because a p-value will vary simply because of differences in sample size or the strength of the association. For example, a very large sample tends to produce very small p-values, while a very small sample tends to produce large p-values. Thus, even weak associations may be considered statistically significant if the sample size is large enough but not statistically significant if the sample size is smaller. Also, a relatively strong association may be accompa-

**Exhibit 8-4**  
**Using P-values to Assess the Potential Effect of Random Error on an Association**

<b>Is <math>p \leq 0.05</math></b>	<b>Is <math>p &gt; 0.05</math></b>
<ol style="list-style-type: none"> <li>1. If YES, the association is <i>statistically significant</i>. The probability of a type I error is equal to or less than 5%, which is the traditional cut-off point (alpha level).</li> <li>2. Random error is an <i>unlikely</i> explanation for the observed association.</li> <li>3. The <i>smaller</i> the p-value, the <i>less likely</i> random error explains the association.</li> <li>4. <i>If the sample size is very large</i>, most associations will be statistically significant, so the association should be judged for its <i>practical significance</i>.</li> </ol>	<ol style="list-style-type: none"> <li>1. If YES, the association is <i>not statistically significant</i>. The probability of a type I error is more than 5%, which is the traditional cut-off point (alpha level).</li> <li>2. Random error is a <i>reasonable</i> explanation for the observed association.</li> <li>3. The <i>larger</i> the p-value, the <i>more likely</i> random error explains the association.</li> <li>4. <i>If the sample size is small</i>, the association should be considered <i>inconclusive</i> due to low power and possible type II error.</li> </ol>

Note: This framework assumes that bias and confounding are not responsible for the finding.

nied by a large p-value because of small sample size. In isolation one cannot be sure if a p-value is more a reflection of sample size or strength of the association or both. Finally, "statistically significant" is often misinterpreted as meaning that the null hypothesis is false or that the association is one of cause and effect. Neither can be demonstrated using statistical significance testing, which depends on probabilities. For these and other reasons most epidemiologists prefer using confidence intervals over statistical significance testing when it comes to assessing random error.<sup>16, 24</sup> The basic methods are discussed in the following section.

#### Assessing Random Error Using Confidence Intervals

Random error can be readily assessed using confidence intervals, which were introduced in chapter 5. This method is referred to as **interval estimation**. Statistically speaking, a confidence interval is constructed around a *point estimate* of the population parameter for a given level of confidence, usually 95 percent. The extent of random error in the estimate is judged by the width of the confidence interval. If the confidence interval is fairly narrow, *and* the confidence level is high, this suggests that there is little random error in the estimate. Therefore, the point estimate can be considered relatively precise. Conversely, if the interval is fairly wide, *and* the confidence level is high, it implies that there is significant random error, and the point estimate can be considered relatively imprecise. Two important caveats need to be kept in mind. First, in assessing the extent of random error it is important to have a

high level of confidence since confidence intervals tend to narrow as the confidence level decreases. It is much easier, for example, to be 50 percent confident that a point estimate falls within a relatively narrow range of values than to be 90 or 95 percent confident. Second, confidence intervals tell us nothing about whether or not a measure of association is valid. Bias or confounding may affect a measure of association no matter how precise it may appear based on a confidence interval.

Assuming there is no significant bias or confounding present, if  $RR = 2.5$ , and the 95%  $CI = 2.1$  to  $2.9$ , we would be reasonably confident that we have a relatively precise estimate of the measure of association, which in this case happens to be a risk ratio. On the other hand, if  $RR = 2.5$ , and the 95%  $CI = 0.6$  to  $19.5$ , we would say that the measure of association appears very imprecise (i.e., subject to substantial random error). These comparisons depend on using the same confidence level, which is usually, but not always, 95 percent. Confidence intervals are best viewed as general indicators of the amount of variability in a measure.<sup>24</sup> If the effects of bias and confounding have been adequately prevented or controlled, however, and if the confidence level is high enough (e.g., 95 percent), then we can be reasonably sure that a narrow confidence interval means that we probably have a relatively accurate measure of association in our study population. Specific methods for calculating confidence intervals for measures of association are discussed in subsequent chapters dealing with specific study designs.

### Confidence Intervals and Significance Testing

Primarily for reasons cited in the previous section, many epidemiologists favor interval estimation over statistical significance testing. Confidence intervals can be used to assess statistical significance, but this is not their attraction, since those who favor confidence intervals do not care to do significance testing. For the record, however, a confidence interval for a risk, rate, odds, or prevalence ratio containing a value of one represents a *non-statistically significant* finding, while a confidence interval *not* containing a value of one represents a *statistically significant* finding. Similarly, a confidence interval for a risk, rate, or prevalence difference containing zero is *not statistically significant*, while one *not* containing zero is *statistically significant*. The value of confidence intervals, however, lies in the fact that they provide information not readily available from significance testing. For one thing, confidence intervals give us a range of possible values for the measure of association.  $RR = 3.4$  (95%  $CI = 0.7$  to  $15.1$ ) indicates that while the point estimate of the population  $RR$  is  $3.4$ , we are 95% confident that the true population  $RR$  ranges from  $0.7$  to  $15.1$ , assuming no systematic errors are present. Furthermore, as stated earlier, we can see from this broad range of values that the estimate is relatively imprecise, and, therefore, we would not want to stake too much on  $RR$  really being  $3.4$ .  $RR = 2.6$  (95%  $CI = 2.1$  to  $3.0$ ), on the other hand, suggests a relatively precise estimate, and we would be relatively confident using  $2.6$  as our estimate of the  $RR$  knowing that we have probably not under- or over-

estimated it by too much, assuming again that there are no systematic errors. Of course, on average, there is still a five percent chance that the true value is really outside this range (i.e., we are after all using a 95 percent versus a 100 percent confidence interval, which would be too broad to be useful). Certainty is just not part of the game plan.

Unlike p-values generated from significance testing, confidence intervals provide clues to the magnitude of an association *and* the precision of the point estimate. This information is lost in p-values.<sup>16</sup> Thus, a 95 percent confidence interval of 0.9 to 11.7 tells us much more than a p-value stated as  $p > 0.05$  or even  $p = 0.07$  when the alpha level is 0.05. With the latter information alone, we would be forced to conclude that the finding is not consistent with the null hypothesis without knowing whether the inconsistency is due to small sample size or a weak or nonexistent association. With the former information, however, we could speculate that the association is probably positive and moderate to strong based on the propensity toward high, positive values in the confidence interval. We could also speculate that the sample size that produced the confidence interval is somewhat small given that the interval is relatively wide. The width of a confidence interval is proportional to sample size, which in turn is proportional to the level of precision, all other factors being equal. Thus, the stated confidence interval appears to reflect significant random error and low precision in the estimate based on its width. Of course, like the selection of the alpha level in statistical significance testing, selection of the confidence level is arbitrary. Also, as with statistical significance testing, interval estimation may be influenced by sources of systematic error, and neither is sufficient for establishing causation between an exposure and outcome. Because of the potential for systematic errors, some recommend that bias and confounding be addressed in a study prior to assessing random error.<sup>21</sup>

In conclusion, confidence intervals, and to a lesser extent p-values, can be used to assess random error in study findings. However, because of the potential for uncontrolled systematic errors and for reasons related to the validity of assumptions regarding the statistical model being employed, these methods are best used to make *qualitative* versus *quantitative* decisions about the *relative* amount of random error.<sup>24</sup> Of these two options, confidence intervals have clear advantages over statistical significance (hypothesis) testing. Why then does hypothesis testing persist? Marks R. Nester<sup>25</sup> has suggested some possible explanations: (a) the appearance of objectivity and exactitude; (b) the availability of easy-to-use statistical software; (c) traditional teaching practices; and (d) demands of certain journal editors or thesis directors. Additionally, he seemed to imply that "peer pressure" may be a factor when he included an explanation that "everyone else seems to use them [tests of hypotheses]."<sup>25(p401)</sup>

### Reducing Random Error

There are two major methods of reducing random error in a study, one of which has already been mentioned.

# Exhibit 144

Ellen Blair Smith, M.D.

Page 1

IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON )  
TALCUM POWDER PRODUCTS )  
MARKETING, SALES )  
PRACTICES, AND PRODUCTS ) MDL NO:  
LIABILITY LITIGATION ) 16-2738 (FLW)(LHG)  
 )  
THIS DOCUMENT RELATES TO )  
ALL CASES )

\*\*\*\*\*

ORAL VIDEOTAPED/REALTIMED DEPOSITION OF

ELLEN BLAIR SMITH, M.D.

JANUARY 9, 2019

VOLUME 1 OF 1

\*\*\*\*\*

Ellen Blair Smith, M.D.

<p style="text-align: right;">Page 2</p> <p>1 ORAL AND VIDEOTAPED/REALTIMED DEPOSITION OF</p> <p>2 ELLEN BLAIR SMITH, M.D., produced as a witness at</p> <p>3 the instance of the Defendants Johnson &amp; Johnson</p> <p>4 entities, and duly sworn, was taken in the</p> <p>5 above-styled and numbered cause on January 9, 2019,</p> <p>6 from 9:24 a.m. to 9:23 p.m., before Karen L. D.</p> <p>7 Schoeve, CSR, RDR, CRR, in and for the State of</p> <p>8 Texas, reported by computerized machine shorthand,</p> <p>9 at the Hilton Austin, 500 E 4th Street, Austin,</p> <p>10 Texas, pursuant to the Federal Rules of Civil</p> <p>11 Procedure and the provisions stated on the record or</p> <p>12 attached hereto.</p> <p>13 It is further agreed that Rule 30(b)(5) is</p> <p>14 waived by agreement of the parties.</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p>	<p style="text-align: right;">Page 4</p> <p>1 A P P E A R A N C E S (Continued)</p> <p>2</p> <p>3 FOR DEFENDANTS JOHNSON &amp; JOHNSON ENTITIES:</p> <p>4 SCOTT A. JAMES, ESQUIRE</p> <p>5 SHOOK, HARDY &amp; BACON L.L.P.</p> <p>6 JPMorgan Chase Tower</p> <p>7 600 Travis Street, Suite 2450</p> <p>8 Houston, Texas 77002-2926</p> <p>9 D: 713.546.5644</p> <p>10 T: 713.227.8008</p> <p>11 F: 713.227.9508</p> <p>12 sjames@shb.com</p> <p>13 --AND--</p> <p>14 KATHERINE McBETH, ESQUIRE</p> <p>15 DRINKER BIDDLE &amp; REATH LLP</p> <p>16 One Logan Square, Suite 2000</p> <p>17 Philadelphia, Pennsylvania 19103-6996</p> <p>18 D: 215.988.2706</p> <p>19 T: 215.988.2700</p> <p>20 F: 215.988.2757</p> <p>21 katherine.mcbeth@db.com</p> <p>22</p> <p>23 FOR DEFENDANT IMERY'S TALC AMERICA, INC.</p> <p>24 MICHAEL R. KLATT, ESQUIRE</p> <p>GORDON REES SCULLY MANSUKHANI, LLP</p> <p>816 Congress Avenue, Suite 1510</p> <p>Austin, Texas 78701</p> <p>D: 512.582.6485</p> <p>T: 512.391.0197</p> <p>F: 512.391.0183</p> <p>mklatt@grsm.com</p> <p>--AND--</p>
<p style="text-align: right;">Page 3</p> <p>1 A P P E A R A N C E S</p> <p>2</p> <p>3 FOR PLAINTIFFS' STEERING COMMITTEE:</p> <p>4 P. LEIGH O'DELL, ESQUIRE</p> <p>5 DR. MARGARET M. THOMPSON, ESQUIRE</p> <p>6 BEASLEY ALLEN, P.C.</p> <p>7 218 Commerce Street</p> <p>8 P.O. Box 4160</p> <p>9 Montgomery, Alabama 36104</p> <p>10 T: 334.269.2343 (Ms. O'Dell)</p> <p>11 F: 334.954.7555 (Ms. O'Dell)</p> <p>12 C: 512.695.1708 (Ms. Thompson)</p> <p>13 T: 800.898.2034 (Ms. Thompson)</p> <p>14 F: 855.674.1818 (Ms. Thompson)</p> <p>15 leigh.odell@beasleyallen.com</p> <p>16 margaret.thompson@beasleyallen.com</p> <p>17 --AND--</p> <p>18 CYNTHIA L. GARBER, ESQUIRE</p> <p>19 ROBINSON CALCAGNIE, INC.</p> <p>20 19 Corporate Plaza Drive</p> <p>21 Newport Beach, California 92660</p> <p>22 C: 949.456.0037</p> <p>23 T: 949.720.1288</p> <p>24 F: 949.720.1292</p> <p>cgarber@robinsonfirm.com</p> <p>--AND--</p> <p>PAULA R. BROWN, ESQUIRE</p> <p>BLOOD HURST &amp; O'REARDON, LLP</p> <p>501 West Broadway, Suite 1490</p> <p>San Diego, California 92101</p> <p>T: 619.338.1100</p> <p>F: 619.338.1101</p> <p>pbrown@bholaw.com</p>	<p style="text-align: right;">Page 5</p> <p>1 A P P E A R A N C E S (Continued)</p> <p>2</p> <p>3 MARK K. SILVER, ESQUIRE</p> <p>4 COUGHLIN DUFFY LLP</p> <p>5 350 Mount Kemble Avenue</p> <p>6 P.O. Box 1917</p> <p>7 Morristown, New Jersey 07962</p> <p>8 D: 973.631.6045</p> <p>9 T: 973.267.0058</p> <p>10 F: 973.267.6442</p> <p>11 msilver@coughlinduffy.com</p> <p>12</p> <p>13 FOR DEFENDANT PERSONAL CARE PRODUCTS COUNCIL:</p> <p>14</p> <p>15 RENEE B. APPEL, ESQUIRE</p> <p>16 SEYFARTH SHAW LLP</p> <p>17 975 F Street, N.W.</p> <p>18 Washington, D.C. 20004</p> <p>19 D: 202.828.5371</p> <p>20 T: 202.463.2400</p> <p>21 F: 202.828.5393</p> <p>22 rappel@seyfarth.com</p> <p>23</p> <p>24 FOR DEFENDANTS PTI ROYSTON LLC AND PTI UNION LLC:</p> <p>TARIQ M. NAEEM, ESQUIRE</p> <p>TUCKER ELLIS   LLP</p> <p>950 Main Avenue, Suite 1100</p> <p>Cleveland, Ohio 44113-7213</p> <p>D: 216.696.3675</p> <p>T: 216.592.5000</p> <p>F: 216.592.5009</p> <p>tariq.naeem@tuckerellis.com</p> <p>ALSO PRESENT:</p> <p>Shane Ramirez, Videographer</p> <p>THE COURT REPORTER:</p> <p>Karen L. D. Schoeve, CRR, RDR, RSA</p>

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<p style="text-align: right;">Page 10</p> <p>1 EXHIBIT INDEX (Continued)</p> <p>2 NO. DESCRIPTION PAGE</p> <p>3 Exhibit 24 226</p> <p>4 Wolters Kluwer Health, Inc., article</p> <p>5 entitled "Genital use of talc and risk</p> <p>6 of ovarian cancer: a meta-analysis"</p> <p>7 by Wera Berge, et al.</p> <p>8 Exhibit 25 238</p> <p>9 Oxford University Press article entitled</p> <p>10 "Perineal Powder Use and Risk of</p> <p>11 Ovarian Cancer" by Serena Houghton,</p> <p>12 et al., dated 06/05/14</p> <p>13 Exhibit 26 254</p> <p>14 Gynecologic Oncology, article</p> <p>15 entitled "Talc and ovarian cancer"</p> <p>16 by Steven A. Narod, dated 2016</p> <p>17 Exhibit 27 300</p> <p>18 List of Tests from 08/22/1985 - 10/1/2002</p> <p>19 Exhibit 28 300</p> <p>20 List of Tests (large blue chart)</p> <p>21 Exhibit 29 309</p> <p>22 MAS, article entitled "The Analysis</p> <p>23 of Johnson &amp; Johnson's Historical</p> <p>24 Baby Powder &amp; Shower to Shower</p> <p>Products from the 1960's to the</p> <p>Early 1990's for Amphibole Asbestos"</p> <p>by William Longo and Mark Rigler,</p> <p>dated 11/14/18</p> <p>Exhibit 30 333</p> <p>European Journal of Cancer Prevention,</p> <p>article entitled "Genital use of talc</p> <p>and risk of ovarian cancer: a meta-analysis"</p> <p>by Wera Berge, et al., dated 05/2018</p> <p>Exhibit 31 352</p> <p>IARC Monographs, Arsenic, Metals,</p> <p>Fibres, and Dusts, Volume 100C,</p> <p>A Review of Human Carcinogens</p>	<p style="text-align: right;">Page 12</p> <p>1 Q. Where are you currently employed,</p> <p>2 Dr. Smith?</p> <p>3 A. I am a hospice medical director for</p> <p>4 Halcyon Home, LLC.</p> <p>5 Q. And do you have a separate consulting</p> <p>6 business?</p> <p>7 A. No.</p> <p>8 Q. We're here to take your deposition today</p> <p>9 in the talc MDL.</p> <p>10 Do you understand that?</p> <p>11 A. I do.</p> <p>12 Q. When were you first contacted about</p> <p>13 serving as an expert witness in the talc MDL?</p> <p>14 A. I was contacted to look at the scientific</p> <p>15 data in January of 2017.</p> <p>16 Q. When did you first agree to serve as an</p> <p>17 expert in the litigation?</p> <p>18 A. In about August or September in 2017.</p> <p>19 Q. Who contacted you?</p> <p>20 A. Margaret Thompson.</p> <p>21 Q. How many contacts have you had with</p> <p>22 Margaret Thompson between the first contact and</p> <p>23 today?</p> <p>24 A. Enumerable.</p>
<p style="text-align: right;">Page 11</p> <p>1 PROCEEDINGS</p> <p>2 THE VIDEOGRAPHER: Here begins the</p> <p>3 deposition of Ellen Blair Smith, Ph.D.</p> <p>4 THE WITNESS: No, M.D.</p> <p>5 THE VIDEOGRAPHER: M.D. Excuse me.</p> <p>6 Today's date is January 9th, 2019.</p> <p>7 The time is 9:24 a.m.</p> <p>8 Will the court reporter please swear</p> <p>9 in the witness.</p> <p>10 ELLEN BLAIR SMITH, M.D.,</p> <p>11 having been first duly sworn to tell the truth, the</p> <p>12 whole truth, and nothing but the truth, so help her</p> <p>13 God, testified as follows:</p> <p>14 EXAMINATION</p> <p>15 BY MR. JAMES:</p> <p>16 Q. Good morning, Dr. Smith.</p> <p>17 A. Good morning.</p> <p>18 Q. Is Dr. Smith the appropriate way to refer</p> <p>19 to you?</p> <p>20 A. Sure.</p> <p>21 Q. Okay. My name is Scott James. I'm</p> <p>22 counsel for J&amp;J, and we met briefly before the</p> <p>23 deposition, correct?</p> <p>24 A. Yes.</p>	<p style="text-align: right;">Page 13</p> <p>1 Q. More than ten?</p> <p>2 A. Yes.</p> <p>3 Q. More than 20?</p> <p>4 A. I would think so.</p> <p>5 Q. All pertaining to this litigation?</p> <p>6 A. No.</p> <p>7 Q. Okay. How do you know Ms. Thompson?</p> <p>8 A. I've known Dr. Thompson for almost 40</p> <p>9 years.</p> <p>10 Q. And how did you first meet Ms. Thompson?</p> <p>11 A. I was a fellow in gynecologic oncology at</p> <p>12 Duke, and she was a senior resident at Duke. She's</p> <p>13 one year behind me in training.</p> <p>14 Q. How many meetings have you had with</p> <p>15 Mrs. Thompson pertaining to this litigation?</p> <p>16 A. I don't know. A lot.</p> <p>17 Q. Same series of questions. More than ten?</p> <p>18 A. Yes.</p> <p>19 Q. Okay. More than 20?</p> <p>20 A. Yes.</p> <p>21 Q. And have those meetings occurred between</p> <p>22 the first contact about the litigation, which was</p> <p>23 January 2017, and today?</p> <p>24 A. Yes.</p>

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<p>1 Q. More than 30 meetings?</p> <p>2 A. Probably not that many.</p> <p>3 Q. Can you estimate the amount of time that</p> <p>4 you have spent with Mrs. Thompson pertaining to the</p> <p>5 issues in this litigation?</p> <p>6 A. No, I cannot.</p> <p>7 Q. Have you met with any other counsel for</p> <p>8 plaintiffs in this litigation?</p> <p>9 A. Leigh O'Dell and Cynthia Garber.</p> <p>10 THE WITNESS: And Paula, I don't know</p> <p>11 your last name.</p> <p>12 MS. BROWN: Brown.</p> <p>13 Q. (BY MR. JAMES) Any other counsel besides</p> <p>14 the ones you just mentioned?</p> <p>15 A. No.</p> <p>16 Q. How much time would you -- have all the</p> <p>17 meetings with Mrs. O'Dell and Ms. Garber -- and I --</p> <p>18 my apologies, Mrs. Brown, have any of those meetings</p> <p>19 been without the presence of Mrs. Thompson?</p> <p>20 A. No.</p> <p>21 Q. Has Ms. Thompson been present at all of</p> <p>22 your meetings pertaining to this litigation?</p> <p>23 A. Yes.</p> <p>24 Q. Dr. Smith, have you given a deposition</p>	<p>1 MR. JAMES: Thank you, Mr. Klatt.</p> <p>2 Q. (BY MR. JAMES) Have you ever worked as an</p> <p>3 expert -- a paid expert in litigation before?</p> <p>4 A. Yes.</p> <p>5 Q. What -- what matters?</p> <p>6 A. It was expert testimony as an expert on</p> <p>7 cervical cancer, in between 1996 and 1998, for a</p> <p>8 local obstetrician gynecologist here in Houston, and</p> <p>9 the case pertained to appropriate treatment of</p> <p>10 carcinoma in situ of the cervix, and the patient's</p> <p>11 informed consent for a hysterectomy.</p> <p>12 Q. Were you serving as an expert for the</p> <p>13 physician?</p> <p>14 A. I was on the defense side, yes, sir.</p> <p>15 Q. Have you served as an expert in any other</p> <p>16 litigation other than the one you just mentioned and</p> <p>17 the talc MDL?</p> <p>18 A. No.</p> <p>19 Q. How many prior depositions have you given?</p> <p>20 A. Maybe five. I was -- I've been treating</p> <p>21 physician in several litigations, not an expert,</p> <p>22 just fact.</p> <p>23 Q. Were you deposed in the -- as an expert in</p> <p>24 the litigation that you just discussed with us?</p>
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<p>1 before?</p> <p>2 A. Yes.</p> <p>3 Q. So you understand the ground rules, but</p> <p>4 I'll repeat just a couple of them to help us along</p> <p>5 the way today, okay?</p> <p>6 A. Okay.</p> <p>7 Q. So my questions will be verbal, and I ask</p> <p>8 that your answers be verbal as well so they can be</p> <p>9 recorded.</p> <p>10 A. Yes.</p> <p>11 Q. If you need a break at any time today,</p> <p>12 please just let me know, and we'll be happy to</p> <p>13 accommodate you.</p> <p>14 A. Thank you.</p> <p>15 Q. And if you don't understand one of my</p> <p>16 questions, please ask me to rephrase, or oftentimes,</p> <p>17 your counsel will ask that I rephrase as well.</p> <p>18 Okay?</p> <p>19 A. Thank you.</p> <p>20 MR. KLATT: And can I add that we have</p> <p>21 an agreement that an objection for one is good for</p> <p>22 all?</p> <p>23 MS. O'DELL: Yes.</p> <p>24 MR. KLATT: Okay. Fine.</p>	<p>1 A. The -- I was --</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 MR. JAMES: Sure.</p> <p>4 MS. O'DELL: Just make sure . . .</p> <p>5 Q. (BY MR. JAMES) So you mentioned that you</p> <p>6 served as an expert one time in one --</p> <p>7 A. Right.</p> <p>8 Q. -- prior case, correct?</p> <p>9 A. Correct.</p> <p>10 Q. Were you deposed in that case?</p> <p>11 A. Yes.</p> <p>12 Q. Were the other -- all of the other</p> <p>13 depositions taken in your capacity as a treating</p> <p>14 physician?</p> <p>15 A. Yes.</p> <p>16 Q. Have you been a defendant in any of those</p> <p>17 cases?</p> <p>18 A. No.</p> <p>19 Q. Are there any other depositions, other</p> <p>20 than the ones that we've just discussed, that you</p> <p>21 have given during your lifetime?</p> <p>22 A. I gave a deposition -- oh, I gave a</p> <p>23 testimony and a deposition once as -- I don't</p> <p>24 exactly know what I was. I'm -- fact, and as a</p>

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<p style="text-align: right;">Page 18</p> <p>1 patient at a hospital.</p> <p>2 Q. Were you a defendant in that case?</p> <p>3 A. No.</p> <p>4 Q. For this case, for the talc MDL, turning</p> <p>5 back to the talc MDL, where do the fees that you</p> <p>6 receive in this litigation, where do those fees go</p> <p>7 to?</p> <p>8 A. You mean come from?</p> <p>9 Q. Do you take -- do you receive those fees</p> <p>10 personally?</p> <p>11 A. Yes, I receive them personally.</p> <p>12 Q. You are currently employed, as we</p> <p>13 discussed, correct?</p> <p>14 A. Yes.</p> <p>15 Q. Do you have any other sources of income</p> <p>16 besides the expert work that you're engaged in now</p> <p>17 and your current role for the hospice facility?</p> <p>18 A. I have several personal annuities.</p> <p>19 Q. Any other sources of income --</p> <p>20 A. No.</p> <p>21 Q. -- besides personal investments?</p> <p>22 A. No.</p> <p>23 Q. And you're charging \$600 per hour in this</p> <p>24 litigation, correct?</p>	<p style="text-align: right;">Page 20</p> <p>1 A. Correct.</p> <p>2 MR. JAMES: And counsel mentioned</p> <p>3 before the deposition that they have brought with</p> <p>4 them copies of the invoices in litigation.</p> <p>5 Could I have those, please.</p> <p>6 MS. O'DELL: Sure.</p> <p>7 MR. JAMES: Thank you.</p> <p>8 MS. O'DELL: I'm missing a last</p> <p>9 invoice. I'll get it to you on the break.</p> <p>10 MR. JAMES: Okay.</p> <p>11 And I'm gonna hand what counsel has --</p> <p>12 I'm gonna mark what counsel has handed me, the set</p> <p>13 of invoices, as Exhibit Number 1.</p> <p>14 (Deposition Exhibit 1 marked for</p> <p>15 identification.)</p> <p>16 Q. (BY MR. JAMES) And, again, Dr. Smith,</p> <p>17 these set of invoices that I was just handed will</p> <p>18 reflect the time that you've spent in this</p> <p>19 litigation through the end of December 2018,</p> <p>20 correct?</p> <p>21 A. When you get the last one, yes, it will.</p> <p>22 Q. Understood.</p> <p>23 And then we get an additional invoice</p> <p>24 for January, correct?</p>
<p style="text-align: right;">Page 19</p> <p>1 A. I am.</p> <p>2 Q. Is that a standard rate regardless of the</p> <p>3 sort of work you're performing?</p> <p>4 A. In this MDL?</p> <p>5 Q. Yes.</p> <p>6 A. Yes.</p> <p>7 Q. Yes, Doctor.</p> <p>8 A. Yes.</p> <p>9 Q. Can you quantify for us the number of</p> <p>10 hours you have spent working as an expert in this</p> <p>11 litigation?</p> <p>12 A. I -- I don't have it off the top of my</p> <p>13 head, but I know they have very clear time records.</p> <p>14 Q. Have you to date invoiced -- have you</p> <p>15 invoiced for all of the time that you've spent in</p> <p>16 the litigation to date?</p> <p>17 A. No.</p> <p>18 Q. Where do your invoices carry you through?</p> <p>19 A. December 31st. I have -- there is an</p> <p>20 invoice that I submitted December 31st that's not</p> <p>21 been paid yet. But I'm through the end of 2018.</p> <p>22 Q. And you'll be submitting an additional</p> <p>23 invoice for the time that you've spent in January,</p> <p>24 correct?</p>	<p style="text-align: right;">Page 21</p> <p>1 A. Correct.</p> <p>2 Q. How much time have you spent in January on</p> <p>3 this litigation?</p> <p>4 MS. O'DELL: Just give your best</p> <p>5 estimate, if you don't . . .</p> <p>6 A. 20. 15 to 20.</p> <p>7 Q. (BY MR. JAMES) Can you break that time</p> <p>8 down for me, as far as what you've been doing during</p> <p>9 the month of January?</p> <p>10 Has it been preparing for the</p> <p>11 deposition, reviewing --</p> <p>12 A. Yes.</p> <p>13 Q. -- articles?</p> <p>14 I'm sorry. I --</p> <p>15 A. Sorry.</p> <p>16 Q. -- didn't finish the question --</p> <p>17 A. I'm sorry.</p> <p>18 Q. -- so let me rephrase it.</p> <p>19 Has all the time that you've spent in</p> <p>20 January been preparing for the deposition?</p> <p>21 A. Yes.</p> <p>22 Q. For the total time that you've spent as</p> <p>23 work for -- strike that.</p> <p>24 For the total time you've spent</p>

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<p>1 working in this litigation as an expert, can you</p> <p>2 give me a rough breakdown about the amount of time</p> <p>3 you've spent reviewing literature, reviewing company</p> <p>4 documents, and meeting with plaintiffs' counsel?</p> <p>5 A. The vast majority of time has -- can I do</p> <p>6 it in percentages?</p> <p>7 Q. That'd -- that would be fine.</p> <p>8 A. Okay. I would say 75 percent is reviewing</p> <p>9 medical literature, 20 percent is meeting with --</p> <p>10 maybe less than that. 15 percent is -- no.</p> <p>11 20 percent is meeting with plaintiffs' attorneys,</p> <p>12 and the remainder is reviewing other documents.</p> <p>13 Q. When you say "other documents," are you</p> <p>14 referring to company docket -- company documents and</p> <p>15 litigation materials you've been provided?</p> <p>16 A. Yes.</p> <p>17 Q. Have you discussed your involvement in</p> <p>18 this litigation with any of the other experts for</p> <p>19 the plaintiffs in the talc MDL?</p> <p>20 A. No.</p> <p>21 Q. And let me ask specifically about a few of</p> <p>22 the experts, if I may.</p> <p>23 Have you discussed this litigation at</p> <p>24 all with Alan Campion?</p>	<p>1 Mr. Campion about the litigation?</p> <p>2 A. Me.</p> <p>3 Q. And before you were retained as a</p> <p>4 litigation, did Ms. -- Ms. Thompson share with you</p> <p>5 any information about the litigation?</p> <p>6 MS. O'DELL: Object to the form.</p> <p>7 A. I'm not sure I understand that question.</p> <p>8 Q. (BY MR. JAMES) What were the nature of</p> <p>9 the discussions before you were retained in this</p> <p>10 litigation with Ms. Thompson?</p> <p>11 A. She informed me that she was involved</p> <p>12 in --</p> <p>13 MS. O'DELL: Let's stop you right</p> <p>14 there. Dr. Smith, in terms of -- should have been</p> <p>15 quicker on my objection.</p> <p>16 In terms of discussions with kind of</p> <p>17 like Dr. Thompson, those are -- those discussions</p> <p>18 are protected by the work prod- -- product</p> <p>19 privilege, so I'm gonna instruct you not to answer</p> <p>20 about any discussions that you had with the lawyers</p> <p>21 for the plaintiffs.</p> <p>22 MR. JAMES: And that's -- just so I'm</p> <p>23 clear, that's regardless of whether the discussions</p> <p>24 were before she was retained or after she was</p>
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<p>1 A. In terms of, "What are you doing?"</p> <p>2 "I'm reading articles," that kind of</p> <p>3 discussion.</p> <p>4 In terms of when he was going to --</p> <p>5 certainly in terms of when he was going out of town</p> <p>6 to do experiments, that kind of discussion.</p> <p>7 But I did give him an article once</p> <p>8 that I didn't understand some of the technology in</p> <p>9 it. And I asked him if he understood it, to read it</p> <p>10 and see if he could explain to me, and he couldn't.</p> <p>11 So I guess that's talking about too.</p> <p>12 Q. Do you recall the article in question?</p> <p>13 A. It was a lab study. I think it was Lee.</p> <p>14 Q. Did you discuss any other studies with</p> <p>15 Alan Campion?</p> <p>16 A. I don't believe so.</p> <p>17 Q. Have you discussed the substance of</p> <p>18 Campion's opinions with him?</p> <p>19 A. No.</p> <p>20 Q. What is your relationship with Alan</p> <p>21 Campion?</p> <p>22 A. He's my husband.</p> <p>23 Q. I understand.</p> <p>24 Did Ms. Thompson first contact you or</p>	<p>1 retained?</p> <p>2 MS. O'DELL: I think, in terms of the</p> <p>3 litigation when she billed for the time regarding</p> <p>4 those discussions, those are privileged. And -- and</p> <p>5 I believe if you'll look at the invoices, Dr. Smith</p> <p>6 has billed for all the time during which she's</p> <p>7 discussed the litigation.</p> <p>8 Q. (BY MR. JAMES) Did -- did you recommend</p> <p>9 to Mrs. Thompson that she also reach out to your</p> <p>10 husband?</p> <p>11 A. Yes.</p> <p>12 Q. And why did you do that?</p> <p>13 A. Leigh O'Dell said that --</p> <p>14 THE WITNESS: Oh, is that work</p> <p>15 product?</p> <p>16 MS. O'DELL: It is, but you can --</p> <p>17 just to the degree I -- I made a suggestion to you,</p> <p>18 but don't go any further than that. Go ahead.</p> <p>19 A. Yeah. Leigh O'Dell told me that the</p> <p>20 defense had recommended evaluation of particles by</p> <p>21 Raman spectroscopy.</p> <p>22 And I said, "Too bad we don't know</p> <p>23 anybody who does that."</p> <p>24 And Leigh and Dr. Thompson both said,</p>

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<p>1 "Yeah, it's too bad." 2 And I said, "My husband does that." I 3 thought they knew. 4 MS. O'DELL: That's the extent of any 5 disclosure, again, of communications with counsel. 6 THE WITNESS: Okay. 7 Q. (BY MR. JAMES) Did you refer Ms. Thompson 8 to any of the other experts who were working on the 9 MDL? 10 A. I did not. 11 Q. Do you understand that there are a number 12 of experts that are working on the MDL for the 13 plaintiffs that are located in Austin? 14 A. I know of one -- oh, I guess two. My 15 husband is one of them. 16 Q. Other than your husband -- 17 A. Yeah. 18 Q. -- do you know of any other experts who 19 are located in Austin? 20 A. One, yes. 21 Q. And who is that? 22 A. Judy Wolf. 23 Q. And do you know Dr. Wolf? 24 A. Yes, I do.</p>	<p>1 litigation? 2 A. No. 3 Q. Have you exchanged any other writings or 4 written materials about this litigation with any of 5 the other experts in this litigation? 6 A. No. 7 Q. How long have you known Dr. Wolf, did you 8 say? 9 A. Maybe 20 years. 10 Q. Did you reach out to her and encourage her 11 involvement in litigation? 12 A. I did not. 13 Q. Did she reach out to you to encourage your 14 involvement -- 15 A. She did not. 16 Q. -- in litigation? 17 THE COURT REPORTER: Doctor, let him 18 finish his whole question, please. 19 THE WITNESS: Yes, ma'am. I'm sorry. 20 Q. (BY MR. JAMES) Have you ever authored any 21 publications concerning talc? 22 A. No, sir. 23 Q. Have you ever authored any publications 24 concerning talc and ovarian cancer?</p>
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<p>1 Q. Do you know here -- did you know her 2 before this litigation? 3 A. Oh, yes. 4 Q. Did you refer Ms. Thompson to her for this 5 litigation? 6 A. I did not. 7 Q. Do you know if Ms. Thompson contacted you 8 or -- or Dr. Wolf first? 9 A. I believe I was contacted first. 10 Q. Have you had any discussions with Dr. Wolf 11 about this litigation? 12 A. No. 13 Q. Have you had discussions with any of the 14 other plaintiffs' experts about this litigation 15 besides Alan Campion? 16 A. No. 17 Q. Are you familiar with a 18 Dr. Clarke-Pearson? 19 A. Very well. 20 Q. Have you had any discussions with 21 Dr. Clarke-Pearson about the litigation? 22 A. No. 23 Q. Have you exchanged any e-mails with any of 24 the experts, including your husband about this</p>	<p>1 A. No, sir. 2 Q. Have you ever authored any publications 3 concerning asbestos? 4 A. No, sir. 5 Q. Have you ever published a talc or asbestos 6 or risk factors for ovarian cancer? 7 A. No. 8 Q. Have you ever conducted any studies that 9 pertain to the issues addressed in your report? 10 MS. O'DELL: Object to the form. 11 A. I am -- 12 THE WITNESS: Can I answer it? 13 MS. O'DELL: Yes. 14 A. I am -- 15 Q. (BY MR. JAMES) May I just rephrase? 16 A. Sure. 17 Q. Have you ever conducted any studies 18 pertaining to the allegation that talc causes 19 ovarian cancer? 20 A. No. 21 Q. Do you -- are you working on any articles 22 that pertain to the issues in this litigation that 23 you consider works in progress? 24 A. No.</p>

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<p style="text-align: right;">Page 30</p> <p>1 Q. Do you have any plans to author or</p> <p>2 contribute to any articles that pertain to the</p> <p>3 issues in this litigation?</p> <p>4 A. No.</p> <p>5 Q. Have you submitted the substance or any --</p> <p>6 any substance in your report to a journal for peer</p> <p>7 review?</p> <p>8 A. No.</p> <p>9 Q. Have you made any internet postings, blog</p> <p>10 postings, or other social media postings about the</p> <p>11 issues in this litigation?</p> <p>12 A. No.</p> <p>13 Q. Have you ever given any presentations,</p> <p>14 speeches, or lectures concerning talc and ovarian</p> <p>15 cancer?</p> <p>16 A. No.</p> <p>17 Q. The same question for asbestos and ovarian</p> <p>18 cancer.</p> <p>19 A. No.</p> <p>20 Q. Have you ever given any interviews or made</p> <p>21 any public statements concerning talc?</p> <p>22 A. No.</p> <p>23 Q. Concerning talc or ovarian cancer?</p> <p>24 A. No.</p>	<p style="text-align: right;">Page 32</p> <p>1 A. Not to my recall.</p> <p>2 Q. Have you ever asked your patients about</p> <p>3 their usage of talcum powder products in taking</p> <p>4 their medical histories?</p> <p>5 A. No.</p> <p>6 Q. And same question: Have you asked -- it's</p> <p>7 not the same question. Let me strike that.</p> <p>8 Have you ever asked your patients</p> <p>9 about their exposure to asbestos in the course of</p> <p>10 taking their medical histories?</p> <p>11 A. No.</p> <p>12 Q. Have you discussed the opinions that</p> <p>13 you've rendered in your report concerning talc and</p> <p>14 ovarian cancer with any of your patients?</p> <p>15 A. No.</p> <p>16 Q. And have you discussed with any of your</p> <p>17 patients the opinions that you've rendered in your</p> <p>18 report concerning asbestos or other alleged</p> <p>19 constituents of talcum powder products?</p> <p>20 A. No.</p> <p>21 Q. Have you ever told any of your patients to</p> <p>22 stop using talcum powder products?</p> <p>23 A. No.</p> <p>24 Q. Have you ever cautioned any of your</p>
<p style="text-align: right;">Page 31</p> <p>1 Q. And concerning asbestos and ovarian</p> <p>2 cancer?</p> <p>3 A. No.</p> <p>4 Q. Have you ever counseled patients on risk</p> <p>5 factors for ovarian cancer?</p> <p>6 A. Yes.</p> <p>7 Q. What risk factors have you counseled your</p> <p>8 patients on?</p> <p>9 A. Predominantly BRCA, Fanconi anemia pathway</p> <p>10 risk factors.</p> <p>11 Q. And when you say "predominantly," are</p> <p>12 there any other risk factors for ovarian cancer that</p> <p>13 you've counseled your patients on?</p> <p>14 A. No.</p> <p>15 Q. Have you ever told a patient that talcum</p> <p>16 powder products was the cause or were the cause of</p> <p>17 their ovarian cancers?</p> <p>18 A. No.</p> <p>19 Q. Have you ever told a patient that talcum</p> <p>20 powder products was likely the cause of their</p> <p>21 ovarian cancer?</p> <p>22 A. No.</p> <p>23 Q. Have you ever asked any of your patients</p> <p>24 about their usage of talcum powder products?</p>	<p style="text-align: right;">Page 33</p> <p>1 patients about using talcum powder products?</p> <p>2 A. No.</p> <p>3 Q. Have you ever evaluated the personal risk</p> <p>4 of a patient for developing ovarian cancer based</p> <p>5 upon their history of usage of talcum powder</p> <p>6 products?</p> <p>7 A. No.</p> <p>8 Q. Have you ever recommended risk-reducing</p> <p>9 surgery on the basis of any of your patients' prior</p> <p>10 usage of talcum powder products?</p> <p>11 A. No.</p> <p>12 Q. Are you aware of any physicians who</p> <p>13 recommend risk-reducing surgery for patients with a</p> <p>14 history of usage of talcum powder products?</p> <p>15 A. There is a published paper using use of</p> <p>16 talcum powder as one of the risk factors for doing</p> <p>17 oophorectomy and benign disease, but I didn't write</p> <p>18 that paper.</p> <p>19 Q. Let me ask the question again. Just make</p> <p>20 sure I said it correctly.</p> <p>21 A. Okay.</p> <p>22 Q. Are you aware of any physicians that you</p> <p>23 know that recommend risk-reducing surgery to</p> <p>24 patients who have prior -- a history of usage of</p>

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<p>1 talcum powder products?</p> <p>2 A. No.</p> <p>3 MS. O'DELL: Object to the form. I</p> <p>4 think the question, Mr. James, is just a little</p> <p>5 unclear. When you say "you know," are you talking</p> <p>6 about know of, know personally --</p> <p>7 MR. JAMES: Sure.</p> <p>8 MS. O'DELL: -- in the community? I</p> <p>9 mean --</p> <p>10 MR. JAMES: Sure. I'll rephrase.</p> <p>11 Q. (BY MR. JAMES) Do you know any physicians</p> <p>12 with whom you have a professional relationship who</p> <p>13 recommend risk-reducing surgery for patients who</p> <p>14 have a prior history of usage of talcum powder</p> <p>15 products?</p> <p>16 A. No.</p> <p>17 Q. You mentioned a paper in the course of --</p> <p>18 of this line of questioning.</p> <p>19 Do you recall the name of the paper</p> <p>20 that you're referring to?</p> <p>21 A. The first author, it starts with a V,</p> <p>22 V-i-t. And the third author is Cramer. And it's</p> <p>23 some --</p> <p>24 Q. Did you say V-i-d, Doctor? I'm sorry.</p>	<p>1 A. I understand that.</p> <p>2 Q. And Dr. Cramer is one of the authors that</p> <p>3 you identified as an author on the paper that you</p> <p>4 were just discussing, correct?</p> <p>5 A. Correct.</p> <p>6 Q. Have you ever recommended increased</p> <p>7 screening or monitoring for your patients for</p> <p>8 ovarian cancer based on their prior usage of talcum</p> <p>9 powder products?</p> <p>10 A. No, I have not.</p> <p>11 Q. Are you aware of any physicians with whom</p> <p>12 you have a professional relationship who do this?</p> <p>13 A. No.</p> <p>14 Q. Have you ever recommended to any doctors</p> <p>15 that you know professionally to tell their patients</p> <p>16 to stop using talcum powder products?</p> <p>17 A. Yes.</p> <p>18 Q. Okay. Who is that?</p> <p>19 A. Which doctors I've recommended that to?</p> <p>20 Q. Yes, Doctor.</p> <p>21 A. Well, I didn't tell them to do it. I told</p> <p>22 them my concerns about talc, but I thought it was</p> <p>23 implicit in expressing my concerns that they would</p> <p>24 counsel their patients. I didn't tell -- I didn't</p>
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<p>1 A. V as in Valentine. V- -- I can't spell</p> <p>2 the name. I can't remember the first name.</p> <p>3 The third author is Daniel Cramer, and</p> <p>4 it was published in 2011 or 2013, and it's -- it's a</p> <p>5 paper about a risk scoring system to recommend</p> <p>6 oophorectomy in women who are undergoing</p> <p>7 hysterectomy, trying to establish their risk of</p> <p>8 ovarian cancer. One of such factors is talcum</p> <p>9 powder use.</p> <p>10 Q. And do you recall if that paper recommends</p> <p>11 that physicians recommend to their patients</p> <p>12 risk-reducing surgery if they have prior history of</p> <p>13 talcum powder product usage?</p> <p>14 A. That is not an exclusive factor in that</p> <p>15 risk assessment system.</p> <p>16 Q. Are you aware of any medical or scientific</p> <p>17 organization that has recommended risk-reducing</p> <p>18 surgery for patients who report prior usage of</p> <p>19 talcum powder products?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A. I am not.</p> <p>22 Q. (BY MR. JAMES) Do you understand that</p> <p>23 Dr. Cramer is a paid litigation expert for the</p> <p>24 plaintiffs?</p>	<p>1 tell the doctors to do a lot of things.</p> <p>2 Q. Understood.</p> <p>3 A. Okay.</p> <p>4 Q. And can you identify any of the doctors</p> <p>5 with whom you've had those conversations?</p> <p>6 A. Yes.</p> <p>7 Q. And please identify them.</p> <p>8 A. Karen Swenson, Michael Breen, Anna Lozano.</p> <p>9 Q. And are those physicians that you know</p> <p>10 here in the Austin community?</p> <p>11 A. Yes.</p> <p>12 Q. Are there any other physicians with whom</p> <p>13 you've discussed your concerns of talcum powder</p> <p>14 products?</p> <p>15 A. Mark Crozier is a GYN, gynecologist, but</p> <p>16 he's no longer practicing. He's retired.</p> <p>17 Q. And do you know if the three physicians</p> <p>18 that you've just identified do now indeed counsel</p> <p>19 their patients about talcum powder products?</p> <p>20 A. I do not know.</p> <p>21 Q. Did you have those conversations with</p> <p>22 those three physicians before your retention in the</p> <p>23 litigation or after?</p> <p>24 A. After.</p>

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<p style="text-align: right;">Page 38</p> <p>1 Q. Have you recommended to those three</p> <p>2 physicians or any other physicians that they</p> <p>3 recommend to their patients risk-reducing surgery if</p> <p>4 they have prior usage of talcum powder products?</p> <p>5 A. No.</p> <p>6 Q. Have you suggested to those three</p> <p>7 physicians or any other physicians that they follow</p> <p>8 some sort of increased monitoring or screening of</p> <p>9 patients based upon prior usage of talcum powder</p> <p>10 products?</p> <p>11 A. No.</p> <p>12 Q. I'm going to hand you a copy of the</p> <p>13 deposition notice, which is why we're all here</p> <p>14 today. And I'm gonna mark that as Exhibit Number 2.</p> <p>15 (Deposition Exhibit 2 marked for</p> <p>16 identification.)</p> <p>17 MS. O'DELL: Thanks, Scott.</p> <p>18 MR. JAMES: Yeah.</p> <p>19 BY MS. O'DELL: We previously served</p> <p>20 objections, and I'll just -- to certain document</p> <p>21 requests that are contained in the notice, and I</p> <p>22 would just reassert those now for the record.</p> <p>23 MR. JAMES: Understood.</p> <p>24 Q. (BY MR. JAMES) Dr. Smith, have you seen a</p>	<p style="text-align: right;">Page 40</p> <p>1 Q. And you've also brought with you a</p> <p>2 separate pile of -- a smaller set of studies or</p> <p>3 literature that you have included some notes on,</p> <p>4 correct?</p> <p>5 A. Correct.</p> <p>6 Q. And without getting up and moving around</p> <p>7 right now, I would like to mark the subset pile as</p> <p>8 Exhibit Number 3.</p> <p>9 MR. JAMES: Okay, Leigh?</p> <p>10 MS. O'DELL: Yeah.</p> <p>11 (Deposition Exhibit 3 marked for</p> <p>12 identification.)</p> <p>13 Q. (BY MR. JAMES) And we'll apply the</p> <p>14 sticker at the break. Okay?</p> <p>15 Dr. Smith, are there any other</p> <p>16 materials that -- that you've brought with you today</p> <p>17 that we have not discussed?</p> <p>18 A. No.</p> <p>19 Q. Are there any other materials that -- that</p> <p>20 having looked back at this deposition notice today,</p> <p>21 that you can think of that are responsive that you</p> <p>22 have not brought with you?</p> <p>23 A. No.</p> <p>24 MS. O'DELL: I say that subject to the</p>
<p style="text-align: right;">Page 39</p> <p>1 copy of this deposition notice before?</p> <p>2 A. Yes.</p> <p>3 Q. And when were you pro- -- when were you</p> <p>4 provided a copy?</p> <p>5 A. Saturday or Sunday -- this past Saturday</p> <p>6 or Sunday.</p> <p>7 Q. And I understand that you and your counsel</p> <p>8 have brought with you to today's deposition a number</p> <p>9 of materials, correct?</p> <p>10 A. Correct.</p> <p>11 Q. And we've discussed and marked the</p> <p>12 invoices already. And so Ms. O'Dell is looking</p> <p>13 toward a table with other materials that I'll</p> <p>14 describe.</p> <p>15 Are those the materials that you've</p> <p>16 brought with you that respond to the deposition</p> <p>17 notice?</p> <p>18 A. Yes, sir.</p> <p>19 Q. And Ms. O'Dell and I discussed prior to</p> <p>20 the deposition, but the materials that you've</p> <p>21 brought with your -- with you today to today's</p> <p>22 deposition are your materials considered in your</p> <p>23 references, correct?</p> <p>24 A. Correct.</p>	<p style="text-align: right;">Page 41</p> <p>1 objections.</p> <p>2 MR. JAMES: Understood.</p> <p>3 Q. (BY MR. JAMES) Okay. I'm going to hand</p> <p>4 you, Dr. Smith, what you have in front of you</p> <p>5 already, and I'm going to mark as Exhibit Number 4 a</p> <p>6 copy of the report that you authored in this</p> <p>7 litigation.</p> <p>8 (Deposition Exhibit 4 marked for</p> <p>9 identification.)</p> <p>10 Q. (BY MR. JAMES) And, Dr. Smith, I'm gonna</p> <p>11 hand you the -- the stickered copy, but I understand</p> <p>12 that you have an identical copy in front of you,</p> <p>13 correct?</p> <p>14 A. Correct.</p> <p>15 Q. And if throughout the deposition today you</p> <p>16 prefer to flip it in the loose-leaf binder, that's</p> <p>17 fine as well. Okay?</p> <p>18 A. Okay. May I --</p> <p>19 MS. O'DELL: Just leave it there.</p> <p>20 A. May I point out a couple of corrections</p> <p>21 for that, because I've only recently --</p> <p>22 MS. O'DELL: Dr. Smith, you certainly</p> <p>23 may, but let him ask you the questions.</p> <p>24 Q. (BY MR. JAMES) Yeah. I'm actually going</p>

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<p>1 to ask you that question, so you'll have a chance</p> <p>2 to.</p> <p>3 A. Okay.</p> <p>4 MR. JAMES: And if counsel, down the</p> <p>5 line throughout the day, has any requests of copies</p> <p>6 of anything I'm handing out, just let me know. I</p> <p>7 have some.</p> <p>8 Q. (BY MR. JAMES) Okay. Dr. Smith, you</p> <p>9 would agree that the report that I've handed you and</p> <p>10 marked as Exhibit Number 4 defines the scope of your</p> <p>11 opinions in this litigation --</p> <p>12 A. Yes.</p> <p>13 Q. -- correct?</p> <p>14 MS. O'DELL: Object to the form.</p> <p>15 Excuse me. I was a little off the mark.</p> <p>16 MR. JAMES: Okay.</p> <p>17 Q. (BY MR. JAMES) Dr. Smith, do you have any</p> <p>18 changes to this report that you'd like to make</p> <p>19 today?</p> <p>20 A. Yes.</p> <p>21 Q. And what are those changes?</p> <p>22 A. There is deficient of second parenthesis,</p> <p>23 and I'm trying to figure out where it is in here.</p> <p>24 Let me go to more substantive things.</p>	<p>1 report?</p> <p>2 A. I did.</p> <p>3 Q. Is all of the wording in this report your</p> <p>4 wording?</p> <p>5 A. Yes.</p> <p>6 Q. Did you consult with Dr. Wolf in writing</p> <p>7 your report?</p> <p>8 A. I did not.</p> <p>9 Q. Did you meet with Dr. Wolf in writing your</p> <p>10 report?</p> <p>11 A. I did not.</p> <p>12 Q. I'm gonna mark as Exhibit Number 5 a copy</p> <p>13 of Dr. Wolf's report in this litigation.</p> <p>14 (Deposition Exhibit 5 marked for</p> <p>15 identification.)</p> <p>16 Q. (BY MR. JAMES) Dr. Smith, have you seen</p> <p>17 this report before?</p> <p>18 A. No.</p> <p>19 MR. JAMES: I apologize to -- to</p> <p>20 counsel and to you, Dr. Smith. I have a bad back</p> <p>21 which prevents me from leaning too --</p> <p>22 A. That's okay.</p> <p>23 Q. -- further -- too far forward.</p> <p>24 Dr. Smith, at first I'd like you to</p>
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<p>1 On page 7 where it says, "A Cancer</p> <p>2 Genome," second paragraph. Do you know where I am,</p> <p>3 page 7, second paragraph?</p> <p>4 Q. Yes. Yes, Doctor.</p> <p>5 A. It should be "The Cancer Genome Atlas,"</p> <p>6 not "A Cancer Genome Atlas."</p> <p>7 Do you want me to mark it on here?</p> <p>8 Q. It's fine.</p> <p>9 A. Okay. And then on the chart labeled on</p> <p>10 Exhibit B the single gene studies, on the second</p> <p>11 page, the back page under Wu, 2015, the fourth</p> <p>12 column, 1.56.</p> <p>13 Are you with me?</p> <p>14 Q. Yes, Doctor.</p> <p>15 A. That 1.56 and 1.77 are inverted. The 1.77</p> <p>16 should go with Hispanics as is the confidence</p> <p>17 intervals. The 1.56 should go with</p> <p>18 African-Americans, as does that conference</p> <p>19 intervals, just a transposition.</p> <p>20 Q. Are there any other changes to the report</p> <p>21 that you'd like to make today?</p> <p>22 A. Well, I haven't found the parentheses yet,</p> <p>23 but you'll figure it out when you see it.</p> <p>24 Q. Okay. Dr. Smith, did you write this</p>	<p>1 pull out your report.</p> <p>2 A. Um-hum.</p> <p>3 Q. And I'd like you to turn to page 16 of</p> <p>4 your report, please.</p> <p>5 A. (Complied.) Um-hum.</p> <p>6 Q. And if you look down at the one, two,</p> <p>7 three, fourth full paragraph.</p> <p>8 A. Um-hum.</p> <p>9 Q. Actually, it's the -- when I say "full,"</p> <p>10 it's the third full paragraph. It's the paragraph</p> <p>11 that starts with "In my opinion."</p> <p>12 A. Um-hum.</p> <p>13 Q. Do you see that paragraph?</p> <p>14 A. Um-hum.</p> <p>15 Q. If you look at that last sentence of that</p> <p>16 paragraph -- I'm gonna read and make sure I read it</p> <p>17 correctly.</p> <p>18 It says, quote, "All of the cohort</p> <p>19 studies are limited by failure to obtain complete</p> <p>20 information, lack of power, selection bias, and</p> <p>21 short follow-up," close quotes.</p> <p>22 Did I read that correctly?</p> <p>23 A. Yes.</p> <p>24 Q. And if you could turn, then, to Dr. Wolf's</p>

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<p>1 report, please.</p> <p>2 A. What page?</p> <p>3 Q. And I'm looking at page 8 of Dr. Wolf's</p> <p>4 report. And it's second full paragraph, so it's the</p> <p>5 second section on that page. I'm gonna quote a page</p> <p>6 of Dr. Wolf's report here.</p> <p>7 A. (Complied.) Um-hum.</p> <p>8 Q. Okay. It's the sentence that starts with</p> <p>9 the word "All."</p> <p>10 Do you see where I am?</p> <p>11 A. Um-hum.</p> <p>12 Q. Okay. It says, quote, "All of the cohort</p> <p>13 study are limited by lack of power, failure to make</p> <p>14 the appropriate queries, selection bias, and short</p> <p>15 follow-up," close quote.</p> <p>16 A. Um-hum.</p> <p>17 Q. Do you see that section that I read?</p> <p>18 A. I do.</p> <p>19 Q. And did I read that correctly?</p> <p>20 A. You did.</p> <p>21 Q. Do you agree that those two sentences are</p> <p>22 remarkably similar?</p> <p>23 A. They are similar.</p> <p>24 Q. And is your testimony that the wording in</p>	<p>1 Q. Okay. And if you look at page -- if you</p> <p>2 can turn to Dr. Wolf's report, please.</p> <p>3 A. Um-hum.</p> <p>4 Q. Okay. If you turn to Dr. Wolf's report on</p> <p>5 page 8 --</p> <p>6 A. Um-hum.</p> <p>7 Q. -- it's the bottom paragraph.</p> <p>8 A. (Complied.)</p> <p>9 Q. And Dr. Wolf starts a paragraph with the</p> <p>10 same phraseology. She says, quote, "When looking at</p> <p>11 epidemiological studies."</p> <p>12 Do you see where I'm reading?</p> <p>13 A. Um-hum.</p> <p>14 Q. And have you had a chance to review her</p> <p>15 paragraph there?</p> <p>16 MS. O'DELL: Object to the form.</p> <p>17 A. (Examined exhibit.) I do.</p> <p>18 Q. (BY MR. JAMES) Okay. Would you agree</p> <p>19 that those two paragraphs are remarkably similar?</p> <p>20 A. I'm not --</p> <p>21 MS. O'DELL: Object to the form.</p> <p>22 A. -- quite through that.</p> <p>23 Q. (BY MR. JAMES) Please take your time.</p> <p>24 I'm sorry.</p>
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<p>1 your report is purely your wording?</p> <p>2 A. It is.</p> <p>3 Q. All right. If you could turn back to your</p> <p>4 report, please, Dr. Smith, on page 16.</p> <p>5 A. (Complied.) I'm on 16. Okay.</p> <p>6 Q. Okay. And if we look down, it's the --</p> <p>7 it's the paragraph below the paragraph that we just</p> <p>8 read. It starts with the "When looking" phrase.</p> <p>9 Do you see --</p> <p>10 A. Um-hum.</p> <p>11 Q. -- where I am?</p> <p>12 A. Um-hum.</p> <p>13 Q. Okay. And if you look at that paragraph,</p> <p>14 Dr. Smith, on page 16, that full paragraph.</p> <p>15 A. Um-hum.</p> <p>16 Q. If you could read that to yourself right</p> <p>17 now, please.</p> <p>18 A. Okay. (Examined exhibit.)</p> <p>19 Q. And it's the paragraph that starts with</p> <p>20 the phrase "When looking at epidemiological</p> <p>21 studies."</p> <p>22 A. Um-hum.</p> <p>23 Q. And have you had a chance to read that?</p> <p>24 A. I have.</p>	<p>1 A. (Examined exhibit.) They're similar. I</p> <p>2 think it's because we looked at the same data.</p> <p>3 Q. And, Dr. Smith, within that paragraph, I'm</p> <p>4 gonna call your attention to two specific sentences.</p> <p>5 So I'm looking back at your report,</p> <p>6 Dr. Smith, and you say, quote -- in your report,</p> <p>7 quote, "Recall and confounding bias in case-control</p> <p>8 studies appear to have minimal impact."</p> <p>9 A. Um-hum.</p> <p>10 Q. "(Penninkilampi and Eslick 2018;" --</p> <p>11 A. Um-hum.</p> <p>12 Q. -- "Langseth 2008)."</p> <p>13 A. Um-hum.</p> <p>14 Q. "There appears to be no significant</p> <p>15 publication bias."</p> <p>16 A. Um-hum.</p> <p>17 Q. "(Berge, 2017;" --</p> <p>18 A. Um-hum.</p> <p>19 Q. -- "Penninkilampi 2018)," close --</p> <p>20 A. Um-hum.</p> <p>21 Q. -- quote.</p> <p>22 Did I read that correctly?</p> <p>23 A. You did.</p> <p>24 Q. And do you see that in Dr. Wolf's report</p>

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<p style="text-align: right;">Page 50</p> <p>1 she has those exact same sentences verbatim?</p> <p>2 A. Yes.</p> <p>3 Q. And, again, is your testimony that the</p> <p>4 wording in this report is your wording?</p> <p>5 A. It is my wording.</p> <p>6 Q. Okay. Dr. Smith, if you could look at</p> <p>7 page 7 of your report. If you look at the bottom</p> <p>8 paragraph, about halfway down through that</p> <p>9 paragraph, Dr. Smith, you state the following --</p> <p>10 A. Page 7?</p> <p>11 Q. Yes, Dr. Smith.</p> <p>12 A. Okay.</p> <p>13 Q. It's the last paragraph on that page,</p> <p>14 right above the visuals.</p> <p>15 A. (Complied.) Um-hum.</p> <p>16 Q. Do you see the sentence that starts with</p> <p>17 the word "binding"? "Binding of BCDX2 or CX3," it's</p> <p>18 a Holliday Junction.</p> <p>19 Do you see where I'm reading?</p> <p>20 A. Um-hum.</p> <p>21 Q. And if I kept rea- -- if I keep reading,</p> <p>22 that sentence ends with a citation to the Compton</p> <p>23 2010 study.</p> <p>24 Do you see that?</p>	<p style="text-align: right;">Page 52</p> <p>1 A. I think it's allowable.</p> <p>2 Q. (BY MR. JAMES) Are there any other</p> <p>3 passages in your report that you can recall that you</p> <p>4 would have written verbatim but not quoted? Excuse</p> <p>5 me, strike that.</p> <p>6 Are there any other passages in your</p> <p>7 report that you have cited to a source and included</p> <p>8 text verbatim from that source --</p> <p>9 MS. O'DELL: Object to the form.</p> <p>10 Q. (BY MR. JAMES) -- that you did not put in</p> <p>11 quotations?</p> <p>12 MS. O'DELL: Excuse me. Object to the</p> <p>13 form.</p> <p>14 A. I don't remember any.</p> <p>15 Q. (BY MR. JAMES) Okay. Dr. Smith, with</p> <p>16 your expert report you produced a copy of your CV.</p> <p>17 A. Yes.</p> <p>18 Q. Correct?</p> <p>19 A. Yes.</p> <p>20 Q. Since providing your counsel with a copy</p> <p>21 of the CV that was then provided to me, have there</p> <p>22 been any changes to your CV?</p> <p>23 A. No.</p> <p>24 Q. I'm gonna mark the CV, then, that was</p>
<p style="text-align: right;">Page 51</p> <p>1 A. Um-hum.</p> <p>2 Q. Is that wording in that sentence your</p> <p>3 wording or is that quoted from the article?</p> <p>4 A. It's quoted from the article, I believe.</p> <p>5 By -- that's why it's referenced.</p> <p>6 Q. Oh, understood. Is that what you were</p> <p>7 referring to earlier as something that was missing a</p> <p>8 quote?</p> <p>9 A. No. No, it's not a quo- -- I -- what I</p> <p>10 was referring to is there's missing a back half of a</p> <p>11 parenthesis in the text.</p> <p>12 Q. Do you agree that if you're quoting</p> <p>13 verbatim from one of the sources that you cite that</p> <p>14 you should include quotations in your report?</p> <p>15 MS. O'DELL: Object to the form.</p> <p>16 A. I'm not sure that's necessary in a</p> <p>17 scientific paper. I think the importance is it's</p> <p>18 cited.</p> <p>19 Q. (BY MR. JAMES) You submitted articles to</p> <p>20 peer-reviewed journals before, correct?</p> <p>21 A. I have.</p> <p>22 Q. And your understanding is that if -- if</p> <p>23 something is cited without quotes that's standard?</p> <p>24 MS. O'DELL: Object to the form.</p>	<p style="text-align: right;">Page 53</p> <p>1 produced to the defendants as Exhibit Number 6.</p> <p>2 (Deposition Exhibit 6 marked for</p> <p>3 identification.)</p> <p>4 Q. (BY MR. JAMES) I'm gonna hand you a copy,</p> <p>5 Dr. Smith. Sorry again for the --</p> <p>6 A. That's okay.</p> <p>7 Q. -- throwing.</p> <p>8 MS. O'DELL: If you just hand them to</p> <p>9 me, I'll be glad to hand them over.</p> <p>10 MR. JAMES: Thank you so much.</p> <p>11 Q. (BY MR. JAMES) And, again, Dr. Smith,</p> <p>12 this is your current CV that you're looking at, is</p> <p>13 Exhibit Number 6?</p> <p>14 A. (Examined exhibit.) Yes, it is.</p> <p>15 Q. Thank you. Okay.</p> <p>16 In your report, Dr. Smith, you</p> <p>17 describe the methodology that you've conducted to</p> <p>18 collect the materials that you reviewed, correct?</p> <p>19 A. Correct.</p> <p>20 Q. And I see you're still looking at your CV,</p> <p>21 so I don't intend to rush you.</p> <p>22 A. That's okay. It's fine.</p> <p>23 Q. And so I am -- I'm not gonna ask you any</p> <p>24 further questions about the CV if you want to set</p>

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<p style="text-align: right;">Page 54</p> <p>1 that aside.</p> <p>2 A. Oh, okay. (Complied.) Okay.</p> <p>3 Q. I'm gonna turn to your report now.</p> <p>4 A. Okay.</p> <p>5 MS. O'DELL: Yeah, just -- we can</p> <p>6 maybe stack -- thank you.</p> <p>7 Q. (BY MR. JAMES) The searches that you ran</p> <p>8 to capture the materials that you reviewed for</p> <p>9 purposes of forming your litigation opinions, had</p> <p>10 you run those searches before being retained as an</p> <p>11 expert in this litigation?</p> <p>12 A. No.</p> <p>13 Q. Had you read any of the studies that you</p> <p>14 cite in your report before being retained in the</p> <p>15 litigation?</p> <p>16 A. Yes.</p> <p>17 Q. Is there a way for you to delineate which</p> <p>18 studies that you reviewed before your retention and</p> <p>19 which studies you reviewed after?</p> <p>20 A. I know I'd seen Cramer 82.</p> <p>21 Do you want me to go through my</p> <p>22 references list and try to identify which one I've</p> <p>23 seen before?</p> <p>24 Q. Well, we understand that the reference</p>	<p style="text-align: right;">Page 56</p> <p>1 any of the studies that are listed in your</p> <p>2 references or materials considered lists?</p> <p>3 A. Yes.</p> <p>4 Q. Is there any way for you to delineate</p> <p>5 which studies were provided to you by plaintiffs'</p> <p>6 counsel and which ones that you found on your own?</p> <p>7 A. Frequently I would provide them an</p> <p>8 abstract asking for full text, so that happened a</p> <p>9 lot. There were some that they sent to me as these</p> <p>10 studies were coming out in e-Pubs, e-publication,</p> <p>11 prior to print publication. I could go through,</p> <p>12 and, again, try to mark those.</p> <p>13 Q. Would you have in your possession records</p> <p>14 that would help you come up with a list of what was</p> <p>15 provided to you versus what you found on your own?</p> <p>16 A. No, but, like, I know that things that</p> <p>17 came out in '17 and '18 usually they got before I</p> <p>18 did.</p> <p>19 Q. And those are the prepub versions you were</p> <p>20 just mentioning?</p> <p>21 A. Right. They usually weren't</p> <p>22 prepublication. They were usually peer --</p> <p>23 Q. You said e-Pub?</p> <p>24 A. Yeah. e-Pub.</p>
<p style="text-align: right;">Page 55</p> <p>1 list is -- is lengthy, correct?</p> <p>2 A. It is.</p> <p>3 Q. Do you think that you're looking for a</p> <p>4 handful of articles or a larger set of articles that</p> <p>5 you saw before your retention?</p> <p>6 A. I would say it's larger than that on these</p> <p>7 references, yes.</p> <p>8 Q. Okay. And so rather than us take the time</p> <p>9 to do that now, Dr. Smith, sitting here today, is</p> <p>10 there any way for you to delineate or define which</p> <p>11 ones you reviewed before being retained?</p> <p>12 A. Do I --</p> <p>13 MS. O'DELL: Object to the -- excuse</p> <p>14 me. Object to the form.</p> <p>15 I think she just -- she's willing to</p> <p>16 do that, if you want her to go through the list,</p> <p>17 but --</p> <p>18 A. Or I can put a check on them, if you want.</p> <p>19 Q. (BY MR. JAMES) Let's not do that right</p> <p>20 now. How about that?</p> <p>21 A. Okay.</p> <p>22 Q. And then we'll think about how we approach</p> <p>23 that.</p> <p>24 Did plaintiffs' counsel provide you</p>	<p style="text-align: right;">Page 57</p> <p>1 Q. My apologies.</p> <p>2 A. Yeah, that didn't have a citation, right.</p> <p>3 Q. In your report under the Methodology</p> <p>4 section, Dr. Smith, you say that you, "Began with a</p> <p>5 comprehensive review of the medical literature," and</p> <p>6 then you use the phraseology, "ON many topics."</p> <p>7 Is that -- do you recall using that</p> <p>8 phraseology? It's at page 2.</p> <p>9 MS. O'DELL: Object to the form.</p> <p>10 A. (Examined exhibit.) I'm looking for -- it</p> <p>11 says --</p> <p>12 Q. (BY MR. JAMES) It's the first sentence,</p> <p>13 Doctor -- it's the second sentence, Dr. Smith.</p> <p>14 A. Then I read many of the references of the</p> <p>15 articles cited in those papers. I didn't see many</p> <p>16 topics.</p> <p>17 Q. Sure. So in the second sentence -- and</p> <p>18 I -- my questioning is probably unnecessarily</p> <p>19 confusing.</p> <p>20 But in the second sentence under</p> <p>21 Methodology, you say that you relied on PubMed</p> <p>22 searches on many topics.</p> <p>23 Do you see that?</p> <p>24 A. Oh, that. Okay. Oh, that was the second</p>

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<p style="text-align: right;">Page 58</p> <p>1 sentence. Sorry, I was off by one. Yes.</p> <p>2 Q. And -- and then later on you just</p> <p>3 mentioned, Dr. Smith, you note in this paragraph</p> <p>4 that you also looked at the references of the</p> <p>5 articles --</p> <p>6 A. Right.</p> <p>7 Q. -- and conducted some additional Google</p> <p>8 searching, correct?</p> <p>9 A. Correct.</p> <p>10 MS. O'DELL: Object to the form.</p> <p>11 Q. (BY MR. JAMES) When you refer to the</p> <p>12 "many topics" there, can you define what many topics</p> <p>13 you are referring to?</p> <p>14 A. Sometimes you find different -- when</p> <p>15 you're using a search engine, even in PubMed, if you</p> <p>16 put in -- put it in one way and it looks like talc</p> <p>17 and ovarian cancer, then you put it in ovarian</p> <p>18 cancer, and talc you may get deferences on how you</p> <p>19 go back. Inflammation in carcinogenesis. Then you</p> <p>20 look at inflammation and ovarian cancer.</p> <p>21 So just, if you word it differently,</p> <p>22 you can pick up different references, and they come</p> <p>23 out in different order sometimes. So it's -- when</p> <p>24 you're looking for everything, you need to, kind of,</p>	<p style="text-align: right;">Page 60</p> <p>1 MS. O'DELL: Object to the form.</p> <p>2 A. I would agree with that.</p> <p>3 Q. (BY MR. JAMES) You agree that --</p> <p>4 THE WITNESS: Am I supposed to wait,</p> <p>5 Laurel [sic]?</p> <p>6 MS. O'DELL: Just give me just a --</p> <p>7 just a second.</p> <p>8 THE WITNESS: Okay.</p> <p>9 MS. O'DELL: I'll try to be quicker on</p> <p>10 the draw.</p> <p>11 THE WITNESS: Okay.</p> <p>12 Q. (BY MR. JAMES) Do you agree that doing</p> <p>13 that is a fundamental first step to your</p> <p>14 methodology?</p> <p>15 A. I do.</p> <p>16 Q. Would you agree that any opinion formed on</p> <p>17 an incomplete review of the relevant scientific and</p> <p>18 medical literature on a particular topic would be</p> <p>19 unreliable?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A. Not necessarily. Not necessarily.</p> <p>22 Q. (BY MR. JAMES) And why do you say that?</p> <p>23 A. I mean, if you miss -- if a person misses</p> <p>24 one article but has a substantial amount of the</p>
<p style="text-align: right;">Page 59</p> <p>1 mix it up and say it different ways to try to find</p> <p>2 all the articles.</p> <p>3 Q. For every topic that you looked at, did</p> <p>4 you conduct a comprehensive review for the</p> <p>5 underlying scientific and medical literature?</p> <p>6 A. Yes.</p> <p>7 Q. So every topic that you've addressed in</p> <p>8 your paper was a critical component of your meth- --</p> <p>9 methodology to conduct a comprehensive review and</p> <p>10 capture all of the relevant and scientific -- the</p> <p>11 relevant scientific and medical literature?</p> <p>12 A. That --</p> <p>13 MS. O'DELL: Object to the form. Give</p> <p>14 me --</p> <p>15 A. That was --</p> <p>16 MS. O'DELL: Excuse me. Just give me</p> <p>17 just a second, and I'll get my obj- -- object to</p> <p>18 the form. Thank you.</p> <p>19 A. That was my attempt.</p> <p>20 Q. (BY MR. JAMES) Do you agree that prior to</p> <p>21 offering expert opinions on particular topics an</p> <p>22 expert should be expected to conduct a con- --</p> <p>23 comprehensive review of the scientific and medical</p> <p>24 literature on that topic?</p>	<p style="text-align: right;">Page 61</p> <p>1 information required, they can reach the right</p> <p>2 conclusion and have not read one article.</p> <p>3 Q. Then do you -- again, do you agree that</p> <p>4 the methodology to opine on a particular topic</p> <p>5 should start with the intent to capture the relevant</p> <p>6 scientific and medical literature on that topic?</p> <p>7 MS. O'DELL: Object to the form.</p> <p>8 A. I agree.</p> <p>9 Q. (BY MR. JAMES) Do you believe that you</p> <p>10 conducted a comprehensive review in the manner that</p> <p>11 we just described on the topic of heavy metals and</p> <p>12 ovarian cancer?</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 A. No.</p> <p>15 Q. (BY MR. JAMES) Do you believe that you</p> <p>16 followed the methodology that we just described on</p> <p>17 the topic of fragrances and ovarian cancer?</p> <p>18 MS. O'DELL: Object to the form.</p> <p>19 A. I read a limited amount of material on</p> <p>20 fragrances.</p> <p>21 Q. (BY MR. JAMES) And so my question</p> <p>22 remains.</p> <p>23 Do you agree -- or do you believe that</p> <p>24 you followed the methodology that we just described</p>

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<p>1 in forming your opinions on fragrances and ovarian 2 cancer? 3 A. No. 4 MS. O'DELL: Object to the form. 5 Q. (BY MR. JAMES) Do you believe that you 6 followed the methodology that we just described in 7 forming your opinions on asbestos and ovarian 8 cancer? 9 MS. O'DELL: Object to the form. 10 A. Yes. 11 Q. (BY MR. JAMES) Do you believe that you 12 followed the methodology that we just described on 13 the issue of, quote, "fibrous talc," close quote, 14 and ovarian cancer? 15 A. Yes. 16 MS. O'DELL: Object to the form. 17 Give me just a second, Doctor. Thank 18 you. 19 Q. (BY MR. JAMES) Dr. Smith, can you explain 20 to me the difference between the reference list 21 attached to your report and the -- what I refer to 22 as the materials considered list attached to your 23 report as part of Exhibit C? 24 Do you understand that there are two</p>	<p>1 referring to as the reliance list and which sources 2 you did not review? 3 A. I'd have to go through it one by one. I'd 4 be glad to. 5 Q. Yeah. I think that we're time limited 6 today, so I ask that we not do that at this time. 7 A. Okay. 8 Q. Are there materials that you reviewed and 9 that you concluded were not relevant to your opinion 10 cited on the reliance list but not on the reference 11 list? 12 MS. O'DELL: Objection to form. 13 A. I think that -- so are we calling the 14 Exhibit C a reliance list -- 15 Q. (BY MR. JAMES) I think, Doctor -- 16 A. -- and my -- 17 Q. I was trying to use your terminology, but 18 it's -- I'll just -- 19 A. Okay. 20 Q. -- to be clearer, I'll ask the question 21 with Exhibit C. 22 A. Okay. 23 Q. Are there materials contained on Exhibit C 24 that you reviewed but did not cite to or discuss in</p>
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<p>1 different lists? 2 A. Yes, I do. 3 Q. Okay. Can you explain to me the 4 difference between those two lists, the significance 5 of why they're placed on one list versus the other? 6 A. If I used a reference in my paper, it is 7 on my reference list. 8 The larger reference list, I believe, 9 is what's called a reliance list that aggregates all 10 the references that all the experts that are 11 involved in this litigation had as one master list 12 of reference for the whole litigation. 13 Does that make sense? 14 Q. Was that a list that you created, the 15 materials considered list? 16 A. The reliance list, the last one? 17 Q. Yes, Doctor. 18 A. I did not create that. 19 Q. Did you review all of the sources listed 20 on that list? 21 A. There are sources on there that I have not 22 reviewed. 23 Q. Is there any way for you to delineate 24 which sources you reviewed on the -- what you're</p>	<p>1 the text of your report? 2 MS. O'DELL: If you understand the 3 question, Doctor. If you're confused about the 4 question, then I'm sure counsel will be glad to 5 rephrase it. Because with the terminology, this is 6 getting -- it is a little confusing. 7 A. Could you clarify that -- 8 Q. (BY MR. JAMES) Sure. I'll try to. 9 A. -- because I am a little confused. 10 Q. I'll try. 11 A. I'm sorry. 12 Q. That's okay. 13 Did you review materials cited on the 14 Exhibit C that you concluded were not relevant to 15 your opinions? 16 A. I can't recall anything. 17 Q. In your report, you make reference to 18 looking at company documents, correct? 19 A. Correct. 20 Q. Did you affirmatively request those 21 company documents or were those provided to you by 22 counsel without you requesting those? 23 A. Those were provided to me without request. 24 Q. Did counsel -- sitting here today, do you</p>

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<p>1 recall the information or subject matter of the</p> <p>2 company documents that you reviewed?</p> <p>3 A. Ummm . . .</p> <p>4 MS. O'DELL: Object to the form.</p> <p>5 If there's any confusion in the</p> <p>6 question, Doctor, just ask him to rephrase it. But</p> <p>7 if you understand the question, feel free to answer.</p> <p>8 A. I believe that the -- there was a</p> <p>9 newspaper article about condoms and exclusion of</p> <p>10 talc products with condoms, that was a company</p> <p>11 document that I saw.</p> <p>12 Q. (BY MR. JAMES) Did the company documents</p> <p>13 that you were provided by counsel inform your</p> <p>14 opinions in this case?</p> <p>15 A. No -- well . . . No.</p> <p>16 Q. When counsel provided you the company</p> <p>17 documents to review, did you ask for any additional</p> <p>18 company documents?</p> <p>19 A. No.</p> <p>20 Q. Did you ask for context to those company</p> <p>21 documents?</p> <p>22 MS. O'DELL: Object- -- objection to</p> <p>23 form of the question.</p> <p>24 You -- don't reveal any communications</p>	<p>1 additional documents that would provide context to</p> <p>2 the documents that you were initially provided?</p> <p>3 A. I --</p> <p>4 MS. O'DELL: Object to the form.</p> <p>5 A. I don't believe so.</p> <p>6 Q. (BY MR. JAMES) Did you ask if any defense</p> <p>7 witness had ever authored any testimony about the</p> <p>8 company documents you were provided?</p> <p>9 MS. O'DELL: Excuse me, Doctor. Don't</p> <p>10 testify to any communications with counsel.</p> <p>11 So if you -- you can ask her, did she</p> <p>12 ask a question. She can say yes. But in terms of</p> <p>13 the subject matter of the question, the content of</p> <p>14 that conversation, I'm gonna object and just</p> <p>15 instruct the witness not to answer.</p> <p>16 Is that -- is that a</p> <p>17 fair distinction --</p> <p>18 MR. JAMES: But you're allowing the</p> <p>19 witness to answer whether she asked for it, correct?</p> <p>20 MS. O'DELL: I think I -- you asked</p> <p>21 that question and I allowed it.</p> <p>22 MR. JAMES: Got it.</p> <p>23 MS. O'DELL: But to the degree you've</p> <p>24 asked for what her questions were, what the</p>
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<p>1 you've had with counsel about company documents, or</p> <p>2 any other thing, for that matter --</p> <p>3 THE WITNESS: Okay.</p> <p>4 MS. O'DELL: -- but in regard to this</p> <p>5 topic.</p> <p>6 MR. JAMES: Well, I'm just asking what</p> <p>7 she's asked to see. So --</p> <p>8 THE WITNESS: I haven't asked to --</p> <p>9 MR. JAMES: -- I'm asking --</p> <p>10 THE WITNESS: -- see anything.</p> <p>11 MR. JAMES: Well, I'm sorry,</p> <p>12 Dr. Smith.</p> <p>13 THE WITNESS: Sorry.</p> <p>14 MR. JAMES: So if you feel like</p> <p>15 there's a way to rephrase my question, that's what</p> <p>16 I'm trying to get at.</p> <p>17 MS. O'DELL: I think you asked -- I</p> <p>18 heard you ask a different question than asked --</p> <p>19 MR. JAMES: Okay. Let me try again.</p> <p>20 MS. O'DELL: -- than that. So just --</p> <p>21 if you don't mind, rephrase it.</p> <p>22 MR. JAMES: Understood.</p> <p>23 Q. (BY MR. JAMES) After you were provided</p> <p>24 the company documents, did you ask if there were any</p>	<p>1 discussion was, I think that is protected.</p> <p>2 MR. JAMES: Got it.</p> <p>3 Q. (BY MR. JAMES) So did you ask for any --</p> <p>4 once you were provided the company documents that</p> <p>5 you were provided by counsel, did you ask whether</p> <p>6 the defense had ever offered any testimony or</p> <p>7 witnesses about the contents of those documents?</p> <p>8 MS. O'DELL: Excuse me, Doctor. Don't</p> <p>9 answer that question.</p> <p>10 That's the subject matter of the</p> <p>11 communication, and I'm not gonna allow her to answer</p> <p>12 those questions.</p> <p>13 So don't answer the question.</p> <p>14 Q. (BY MR. JAMES) Do you know if any defense</p> <p>15 witness has ever addressed the content of the</p> <p>16 company documents that you were provided by counsel?</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 A. I don't know that.</p> <p>19 Q. (BY MR. JAMES) You would agree with me</p> <p>20 that if you were attempting as a scientist to form</p> <p>21 opinions on a particular topic you would want to be</p> <p>22 sure that you were provided both sides of the story,</p> <p>23 correct?</p> <p>24 MS. O'DELL: Object to the form.</p>

18 (Pages 66 to 69)

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<p>1           You may answer the question if you</p> <p>2   understand it, Doctor.</p> <p>3       A. I think the scientific literature presents</p> <p>4   both sides of the story. That's how you factor it</p> <p>5   in, right? You usually don't call up individuals</p> <p>6   and ask them their opinion. Their published,</p> <p>7   peer-reviewed opinions are available in the</p> <p>8   literature.</p> <p>9       Q. (BY MR. JAMES) Dr. Smith, in your report</p> <p>10   in discussing asbestos, you mentioned litigation</p> <p>11   reports authored by a Dr. Longo, correct?</p> <p>12      A. Yes.</p> <p>13      Q. Okay. So we were just talking about</p> <p>14   company documents --</p> <p>15      A. But now --</p> <p>16      Q. -- in the -- prior to the questioning, and</p> <p>17   I want to just make sure you know where I'm going.</p> <p>18       You testified that the company</p> <p>19   documents did not inform your opinions, correct?</p> <p>20       MS. O'DELL: Object to the form.</p> <p>21      A. Yes. Perhaps you and I are talking about</p> <p>22   different things between company documents and</p> <p>23   litigation documents.</p> <p>24      Q. (BY MR. JAMES) Sure. And I think -- fair</p>	<p>1       A. I do not know that.</p> <p>2       Q. And wouldn't you want to know that as a</p> <p>3   scientist before forming opinions upon Dr. Longo's</p> <p>4   reports?</p> <p>5       MS. O'DELL: Object to the form.</p> <p>6      A. I would be interested in that.</p> <p>7       Q. (BY MR. JAMES) And counsel didn't provide</p> <p>8   that information to you, did they?</p> <p>9      A. They did not.</p> <p>10       MS. O'DELL: I would just object to</p> <p>11   the statement that somehow that question assumes,</p> <p>12   Counsel, that defense -- defendants in this case</p> <p>13   have served expert reports, which they have not.</p> <p>14   It's a little misleading, but . . .</p> <p>15      Q. (BY MR. JAMES) You were looking at</p> <p>16   Dr. Longo's litigation reports from other cases.</p> <p>17       Did you know that?</p> <p>18       MS. O'DELL: Dr. Smith is not involved</p> <p>19   in other cases, so I'm not sure she would have</p> <p>20   information to know what's another case or what the</p> <p>21   present case. So to be fair --</p> <p>22       MR. JAMES: Leigh, I've asked a fair</p> <p>23   question, and I think Dr. Smith is capable of</p> <p>24   answering it.</p>
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<p>1   enough.</p> <p>2       Let's just move on to the Longo</p> <p>3   requesting.</p> <p>4      A. Okay.</p> <p>5       Q. And with respect to asbestos, you looked</p> <p>6   at Longo litigation reports, correct?</p> <p>7      A. I did.</p> <p>8       Q. You understand those to be litigation</p> <p>9   materials, correct?</p> <p>10     A. Yes.</p> <p>11       MS. O'DELL: Object to the form.</p> <p>12      Q. (BY MR. JAMES) Do you understand Longo --</p> <p>13   Dr. Longo is a paid litigation expert, correct?</p> <p>14     A. Yes.</p> <p>15      Q. And you understand his reports are not</p> <p>16   peer-reviewed, correct?</p> <p>17       MS. O'DELL: Object to the form.</p> <p>18     A. Yes.</p> <p>19      Q. (BY MR. JAMES) You understand that</p> <p>20   they're not published, correct?</p> <p>21     A. Yes.</p> <p>22      Q. Do you know if anyone on the defense side</p> <p>23   has addressed or responded to Dr. Longo's litigation</p> <p>24   reports?</p>	<p>1       MS. O'DELL: I'm not sure that that's</p> <p>2   a fair question.</p> <p>3       If you understand it --</p> <p>4       MR. JAMES: Well, why don't you please</p> <p>5   state your objection and then let Dr. Smith answer,</p> <p>6   if you can.</p> <p>7       MS. O'DELL: Object to the form.</p> <p>8       MR. JAMES: Thank you.</p> <p>9      A. Could you say it again? I got lost.</p> <p>10     Q. (BY MR. JAMES) Sure. You've already</p> <p>11   agreed with me that the Longo reports that you've</p> <p>12   reviewed are litigation reports, correct?</p> <p>13     A. Right.</p> <p>14      Q. Okay. And your counsel just stated that</p> <p>15   the Longo litigation reports were not part of the</p> <p>16   MDL litigation.</p> <p>17       MS. O'DELL: That's not what I said.</p> <p>18       MR. JAMES: Okay.</p> <p>19      Q. (BY MR. JAMES) Nevertheless, you have</p> <p>20   reviewed litigation reports from plaintiffs -- an</p> <p>21   expert that's paid by plaintiffs in this litigation,</p> <p>22   correct?</p> <p>23     A. I have.</p> <p>24      Q. You have also reviewed a litigation report</p>

19 (Pages 70 to 73)

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<p>1 prepared by a Dr. Crowley, correct?</p> <p>2 A. Correct.</p> <p>3 Q. And that pertains to fragrances, correct?</p> <p>4 A. Correct.</p> <p>5 Q. You understand Dr. Crowley's report is not</p> <p>6 peer-reviewed, correct?</p> <p>7 A. Correct.</p> <p>8 Q. You understand his report is not published</p> <p>9 in the medical literature, correct?</p> <p>10 A. Correct.</p> <p>11 Q. Did you review any of the other expert</p> <p>12 reports besides Dr. Crowley's report in this MDL?</p> <p>13 MS. O'DELL: In addition to Dr. Longo.</p> <p>14 MR. JAMES: Thank you.</p> <p>15 Q. (BY MR. JAMES) In addition to Dr. Longo?</p> <p>16 A. I don't think so.</p> <p>17 MS. O'DELL: Hey, Scott, we've been</p> <p>18 going about an hour and 15 minutes or something</p> <p>19 close to that, hour and 10 minutes. Whenever it's a</p> <p>20 good place --</p> <p>21 MR. JAMES: Another 5 to finish this</p> <p>22 line.</p> <p>23 Is that good, Doctor?</p> <p>24 THE WITNESS: Sure.</p>	<p>1 Dr. Blount has been listed by plaintiffs in talc</p> <p>2 litigation as an expert for plaintiffs?</p> <p>3 MS. O'DELL: Object to the form;</p> <p>4 misstates the testimony, as I understand it.</p> <p>5 A. I know she's been deposed.</p> <p>6 Q. (BY MR. JAMES) Did you review her</p> <p>7 testimony in full?</p> <p>8 A. I -- I reviewed her paper, and I read her</p> <p>9 testimony fairly superficially.</p> <p>10 Q. Do you know if the defense in the talc</p> <p>11 litigation has responded to or addressed</p> <p>12 Dr. Blount's testimony and article?</p> <p>13 A. I do not know that.</p> <p>14 Q. Wouldn't you like to know that?</p> <p>15 MS. O'DELL: Object to the form.</p> <p>16 A. Sure.</p> <p>17 Q. (BY MR. JAMES) Is there a reason that you</p> <p>18 didn't consider the defenses' response to</p> <p>19 Dr. Blount's testimony and article?</p> <p>20 MS. O'DELL: Object to the form of the</p> <p>21 question.</p> <p>22 There have been no expert reports</p> <p>23 in -- by -- served by defendants in the MDL. That's</p> <p>24 an unfair question.</p>
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<p>1 MR. JAMES: Okay.</p> <p>2 Q. (BY MR. JAMES) Dr. Smith, you also looked</p> <p>3 at -- or at least you listed, in your lists, you</p> <p>4 looked at the deposition of a Dr. Alice Blount,</p> <p>5 correct?</p> <p>6 A. Oh, yes.</p> <p>7 Q. Okay. Does that ring a bell?</p> <p>8 A. Yes. But is she involved in this</p> <p>9 litigation?</p> <p>10 Q. That was gonna be my question to you.</p> <p>11 Did you know that Dr. Blount has</p> <p>12 testified as an expert for plaintiffs in the talc</p> <p>13 litigation?</p> <p>14 A. In --</p> <p>15 MS. O'DELL: Excuse me. Object to the</p> <p>16 form.</p> <p>17 A. In this MDL?</p> <p>18 Q. (BY MR. JAMES) In the talc litigation --</p> <p>19 A. Oh, in the talc litigation, yes.</p> <p>20 MS. O'DELL: Object to the form. I</p> <p>21 think it's a mischaracterization to say she's an</p> <p>22 expert, to my knowledge.</p> <p>23 So you want to restate your question.</p> <p>24 Q. (BY MR. JAMES) Do you know that</p>	<p>1 A. I'm lost again. I'm sorry.</p> <p>2 Q. (BY MR. JAMES) Sure. I understand.</p> <p>3 You read Dr. Blount's testimony</p> <p>4 superficially is what you just testified to,</p> <p>5 correct?</p> <p>6 A. Yes.</p> <p>7 Q. You understand Dr. Blount testified in</p> <p>8 another case in the talc litigation, correct?</p> <p>9 A. Yes.</p> <p>10 Q. Do you know if the defendants responded to</p> <p>11 Dr. Blount's testimony and report in that case?</p> <p>12 A. I do not know that.</p> <p>13 Q. You've cited in your report a deposition</p> <p>14 exhibit from a Dr. John Hopkins.</p> <p>15 Does that ring a bell?</p> <p>16 A. It does.</p> <p>17 Q. Okay. And you also cited a deposition</p> <p>18 exhibit from a Julie Pier.</p> <p>19 Does that ring a bell?</p> <p>20 A. It does.</p> <p>21 Q. And why did you look at those two</p> <p>22 exhibits?</p> <p>23 A. I looked at the identification in Pier on</p> <p>24 minerals and quantities, parts per million.</p>

20 (Pages 74 to 77)

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<p style="text-align: right;">Page 78</p> <p>1 I looked at the Hopkins', the</p> <p>2 identification of asbestos and asbestiform species</p> <p>3 in various ore and talcum powder products.</p> <p>4 Q. Did you consider both of those exhibits</p> <p>5 relevant to the opinions that you formed concerning</p> <p>6 asbestos and ovarian cancer?</p> <p>7 A. Yes.</p> <p>8 Q. Did you -- do you know if the defense has</p> <p>9 addressed or responded to the information contained</p> <p>10 in those two deposition exhibits?</p> <p>11 A. I --</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A. I do not know.</p> <p>14 Q. (BY MR. JAMES) Did you ask if the</p> <p>15 defendants have responded to the information</p> <p>16 contained in those exhibits?</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 A. I did --</p> <p>19 MS. O'DELL: And I -- excuse me. And</p> <p>20 I would instruct you just-- he's asking you about</p> <p>21 what you talked about with your lawyers for the</p> <p>22 plaintiffs, and I would just instruct you not to</p> <p>23 answer that question, as I've instructed you on</p> <p>24 every other line of inquiry to that extent.</p>	<p style="text-align: right;">Page 80</p> <p>1 Dr. Smith, did you do any independent</p> <p>2 testing to support your opinions in this case?</p> <p>3 A. I did not.</p> <p>4 Q. Did you do any independent analysis or</p> <p>5 reanalysis of raw data to support your opinions?</p> <p>6 A. I did not.</p> <p>7 Q. On page 2 of your report, Dr. Smith, you</p> <p>8 conclude with a passage where you state that you</p> <p>9 have applied in this litigation, quote, "The same</p> <p>10 methodology and scientific rigor that I have used</p> <p>11 regularly in my professional career and clinical</p> <p>12 practice," closed quote.</p> <p>13 Do you see that passage that I read?</p> <p>14 A. Oh, yes. In the -- under Methodology?</p> <p>15 Q. Yes, Doctor.</p> <p>16 A. Yes.</p> <p>17 Q. Did you see where I read?</p> <p>18 A. Yes.</p> <p>19 Q. Okay.</p> <p>20 A. Yes.</p> <p>21 Q. In your professional practice and your</p> <p>22 clinical practice, do you rely on litigation reports</p> <p>23 by paid experts?</p> <p>24 MS. O'DELL: Object to the form.</p>
<p style="text-align: right;">Page 79</p> <p>1 I instructed her not to answer that.</p> <p>2 A. I'm --</p> <p>3 MR. JAMES: Understood.</p> <p>4 A. -- not responding.</p> <p>5 Q. (BY MR. JAMES) Yeah, understood.</p> <p>6 Would you like to know if the</p> <p>7 defendants have responded to the information</p> <p>8 contained in the two deposition exhibits that you</p> <p>9 cited?</p> <p>10 A. Yes, I would.</p> <p>11 MR. JAMES: Is now good for a break?</p> <p>12 MS. O'DELL: Sure.</p> <p>13 MR. JAMES: Okay.</p> <p>14 Thank you, Doctor.</p> <p>15 THE VIDEOGRAPHER: Going off the</p> <p>16 record. The time is 10:34 a.m.</p> <p>17 (A recess was taken from 10:34 a.m.</p> <p>18 to 10:53 a.m.)</p> <p>19 THE VIDEOGRAPHER: Back on the record.</p> <p>20 The time is 10:53 a.m.</p> <p>21 Q. (BY MR. JAMES) Okay. Dr. Smith, are we</p> <p>22 ready to proceed?</p> <p>23 A. I am.</p> <p>24 Q. Great.</p>	<p style="text-align: right;">Page 81</p> <p>1 A. No.</p> <p>2 Q. (BY MR. JAMES) Do you rely on unpublished</p> <p>3 data or unpublished testing as a clinician?</p> <p>4 MS. O'DELL: Object to the form.</p> <p>5 A. Occasionally, there is unpublished data</p> <p>6 that you may cite information from an author for the</p> <p>7 things that weren't in publication material.</p> <p>8 That -- that happens commonly with a lot of</p> <p>9 scientific reports.</p> <p>10 Q. (BY MR. JAMES) As a clinician, have you</p> <p>11 ever relied on the type of litigation materials that</p> <p>12 you have reviewed in your capacity as an expert in</p> <p>13 this case?</p> <p>14 MS. O'DELL: Object to the form;</p> <p>15 vague.</p> <p>16 A. I don't think so.</p> <p>17 Q. (BY MR. JAMES) As a clinician, in your</p> <p>18 daily practice or your professional practice, have</p> <p>19 you ever relied on deposition testimony of paid</p> <p>20 experts to form your opinions?</p> <p>21 MS. O'DELL: Object to the form.</p> <p>22 A. No.</p> <p>23 Q. (BY MR. JAMES) Before being contacted by</p> <p>24 counsel in this case, had you formed an opinion as</p>

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<p>1 to any cause of ovarian cancer?</p> <p>2 A. (No response.)</p> <p>3 Q. And let me rephrase that --</p> <p>4 A. Yes.</p> <p>5 Q. -- because it's prob- -- it's phrased</p> <p>6 poorly.</p> <p>7 Before being contacted about work in</p> <p>8 this litigation, had you reached the conclusion that</p> <p>9 there were any causes of ovarian cancer?</p> <p>10 A. Yes.</p> <p>11 Q. And what had you concluded before being</p> <p>12 contacted in the litigation about causes of ovarian</p> <p>13 cancer?</p> <p>14 A. Well, I'm not sure that I</p> <p>15 understand how -- what do you mean "cause"?</p> <p>16 Q. You understand that in the epidemiologic</p> <p>17 literature, the word "association" is used, correct?</p> <p>18 A. Yes.</p> <p>19 Q. And the word "cause" is used, correct?</p> <p>20 A. Correct.</p> <p>21 Q. In your clinical practice, if someone</p> <p>22 asked you what caused their ovarian cancer, would</p> <p>23 you know what they were asking you?</p> <p>24 A. Yes.</p>	<p>1 loosely, could -- could be categorized as a cause of</p> <p>2 ovarian cancer?</p> <p>3 A. Yes.</p> <p>4 Q. Is there anything else that you had</p> <p>5 concluded before your work in this litigation that</p> <p>6 could be categorized as a cause of ovarian cancer?</p> <p>7 A. Yes.</p> <p>8 Q. What else?</p> <p>9 A. Endometriosis.</p> <p>10 Do you want more?</p> <p>11 Q. Yes. If you could list any others.</p> <p>12 A. Nulliparity, some data on obesity, mixed</p> <p>13 data on pelvic inflammatory disease, mixed data on</p> <p>14 smoking. That's what has come to the top of my</p> <p>15 head.</p> <p>16 Q. And just to make sure that we're on the</p> <p>17 same page, my question at this point is still</p> <p>18 confined to the issue of cause.</p> <p>19 And so of the items that you just</p> <p>20 mentioned before being retained in this litigation,</p> <p>21 had you concluded that obesity is a cause of ovarian</p> <p>22 cancer?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A. Mixed data on that. More pertaining to</p>
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<p>1 Q. By the word "cause"?</p> <p>2 A. Yes.</p> <p>3 Q. And so I don't mean for my question to be</p> <p>4 confusing. I'm -- what I'm asking you is if --</p> <p>5 certainly in this litigation, you have offered the</p> <p>6 opinion in your report that in your opinion talc</p> <p>7 causes ovarian cancer, correct?</p> <p>8 A. Correct.</p> <p>9 Q. Did you form that opinion, that causation</p> <p>10 opinion, after being retained in this litigation?</p> <p>11 A. After reviewing the literature.</p> <p>12 Q. And after being retained; is that right?</p> <p>13 A. Correct.</p> <p>14 Q. And so my question to you, which I hope is</p> <p>15 simple, is that before you were contacted about work</p> <p>16 in this litigation, had you concluded that there was</p> <p>17 anything else out there that could be categorized as</p> <p>18 a cause of ovarian cancer?</p> <p>19 A. Are you -- causation such as genetic</p> <p>20 predisposition?</p> <p>21 Q. That would be one of them.</p> <p>22 A. Okay. Yeah. Then we're on the same page.</p> <p>23 Q. Okay. And so had -- had you concluded</p> <p>24 before your work in this litigation that genetics,</p>	<p>1 endometrioid cancers.</p> <p>2 Q. (BY MR. JAMES) So you would -- did you</p> <p>3 hold the opinion before your work in this litigation</p> <p>4 that obesity was a cause of ovarian cancer?</p> <p>5 MS. O'DELL: Object to the form.</p> <p>6 A. Partially.</p> <p>7 Q. (BY MR. JAMES) And when you say</p> <p>8 "partially," are you referring to the subtype?</p> <p>9 A. Yes.</p> <p>10 Q. And so of the i- -- the items that you did</p> <p>11 just mention to me, then, you do consider those to</p> <p>12 be -- you did consider those to be causes of ovarian</p> <p>13 cancer before your work in this litigation; is that</p> <p>14 correct?</p> <p>15 A. Correct.</p> <p>16 Q. When you reached those causation</p> <p>17 conclusions, did you do so based upon the body of</p> <p>18 scientific and medical literature?</p> <p>19 A. Yes.</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 Q. (BY MR. JAMES) Did you reach those</p> <p>22 conclusions in the context of litigation?</p> <p>23 A. No.</p> <p>24 Q. Did you reach those causation conclusions</p>

22 (Pages 82 to 85)

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<p>1 after talking with plaintiffs' counsel?</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 A. No.</p> <p>4 Q. (BY MR. JAMES) Did you reach those</p> <p>5 causation conclusions after being provided materials</p> <p>6 selected for your review by counsel?</p> <p>7 MS. O'DELL: Object to the form.</p> <p>8 A. (Examined realtime screen.) No.</p> <p>9 Q. (BY MR. JAMES) Did you reach those</p> <p>10 causation conclusions by reviewing unpublished</p> <p>11 litigation reports?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A. No.</p> <p>14 Q. (BY MR. JAMES) Did you reach those</p> <p>15 causation conclusions by reviewing company</p> <p>16 documents?</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 A. No.</p> <p>19 Q. (BY MR. JAMES) What conclusions did you</p> <p>20 have, if any, before your work in this litigation on</p> <p>21 the talc ovarian cancer hypothesis?</p> <p>22 MS. O'DELL: Object to the form.</p> <p>23 Would you -- would you -- could you</p> <p>24 just -- I was just reading your question, Scott.</p>	<p>1 Q. (BY MR. JAMES) When you said you</p> <p>2 registered those concerns in your brain, what do you</p> <p>3 mean by that?</p> <p>4 A. I never used talcum powder products on my</p> <p>5 female children, and I don't have any male children,</p> <p>6 so that's pretty much -- and I didn't use talcum</p> <p>7 powder products on myself, and I felt strongly about</p> <p>8 that.</p> <p>9 Q. And what time frame was that?</p> <p>10 A. Well, I heard from him in 1979 in my first</p> <p>11 trial, and I didn't use talcum powder from 1979 to</p> <p>12 1992 when my first daughter was born, nor did I use</p> <p>13 it in 1994 for diapering my second daughter; and we</p> <p>14 just didn't have powder in my home.</p> <p>15 Q. Did you express those concerns in writing</p> <p>16 anywhere?</p> <p>17 A. No.</p> <p>18 Q. We discussed this already this morning,</p> <p>19 but did you express those concerns to any of the</p> <p>20 patients that you treated?</p> <p>21 A. No.</p> <p>22 Q. Same line of questions but with respect to</p> <p>23 asbestos. Okay?</p> <p>24 Did you conclude before -- what --</p>
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<p>1 Is that right?</p> <p>2 MR. JAMES: What conclusions.</p> <p>3 MS. O'DELL: Okay. Sorry.</p> <p>4 A. I was concerned about talc products being</p> <p>5 transported through the female genital tract because</p> <p>6 of findings in the '70s of talc deeply embedded in</p> <p>7 ovarian tissue.</p> <p>8 J. Don Woodruff was one of my mentors,</p> <p>9 and he shared this information with me in 1979; and</p> <p>10 I found it concerning. He went on or was in the</p> <p>11 position at that time of postulating talc -- talcum</p> <p>12 powder as an etiologic factor in the development of</p> <p>13 ovarian cancer. This is well before the publication</p> <p>14 of the epidemiologic studies, and I registered his</p> <p>15 concerns in my brain.</p> <p>16 Q. (BY MR. JAMES) And with that statement,</p> <p>17 then, are you indicating that those concerns -- you</p> <p>18 did not express those concerns to anyone else,</p> <p>19 correct?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 Misstates her testimony, but go ahead.</p> <p>22 MR. JAMES: I don't want to do that,</p> <p>23 so let me start over.</p> <p>24 A. Okay.</p>	<p>1 what conclusions had you come to, if any, before</p> <p>2 your work in this litigation about a relationship</p> <p>3 between asbestos and ovarian cancer?</p> <p>4 A. Prior to my work in this litigation, I did</p> <p>5 not have an awareness of the relationship of</p> <p>6 asbestos to ovarian cancer.</p> <p>7 Q. Is that an opinion, then, that you've</p> <p>8 formed in the context of litigation?</p> <p>9 MS. O'DELL: Object to the form.</p> <p>10 A. After my review of the scientific data,</p> <p>11 yes.</p> <p>12 Q. (BY MR. JAMES) And to be clear and to</p> <p>13 respond to the objection, the question I'm asking</p> <p>14 is: Did you reach the opinion about the</p> <p>15 relationship between asbestos and ovarian cancer in</p> <p>16 the context of this litigation?</p> <p>17 A. I think it's unfair to say "context of</p> <p>18 litigation." I would have -- had I reviewed all</p> <p>19 that literature, I would have reached that</p> <p>20 conclusion whether or not this litigation was</p> <p>21 ongoing or not.</p> <p>22 Q. If you don't like the word "context," I</p> <p>23 can rephrase.</p> <p>24 Did you reach the asbestos conclusions</p>

23 (Pages 86 to 89)

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<p>1 that you've rendered in your report after being 2 retained in this litigation? 3 A. Yes, correct. 4 Q. On that note, Dr. Smith, let's look at 5 page 21 of your report, please. 6 A. (Complied.) Excuse me. 7 Q. And you see at the bottom of page 21, 8 Dr. Smith, you have a section that's labeled 9 "Summary of my opinions." 10 Do you see where I am? 11 A. Yes, sir. 12 Q. And Item Number 1 is the opinion that you 13 hold today that talc causes ovarian cancer, correct? 14 A. Correct. 15 Q. And we've discussed this already, but that 16 is an opinion that you've formed after being 17 retained in the litigation, correct? 18 A. Correct. 19 Q. With respect to Item Number 2, you have 20 opined that "There is credible evidence that 21 Johnson and Johnson baby powder products contain 22 asbestos." 23 Do you see where I read? 24 A. I do.</p>	<p>1 those are facts. Those are scientific facts. 2 They've been demonstrated in the laboratory. 3 Q. (BY MR. JAMES) You understand that you 4 have been retained to offer your scientific opinions 5 in this litigation, right? 6 A. Yes. Yes. 7 Q. And so Number 3, do you hold the opinion 8 that you've expressed in Number 3? 9 A. Yes. 10 Q. Is that an opinion that you've formed 11 after being retained in the litigation? 12 A. Yes. 13 Q. And Number 4, do you see where I am still? 14 A. I do. 15 Q. Okay. And Number 4 is an opinion 16 concerning migration and also an opinion concerning 17 inhalation, correct? 18 A. Yes. 19 Q. Are those opinions that you've formed 20 after being retained in this litigation? 21 A. Correct. 22 Q. Turning to the opinion that you have 23 expressed that there is, quote, "credible evidence," 24 close quote, that Johnson's Baby Powder products</p>
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<p>1 Q. Is that an opinion that you formed after 2 your retention in this litigation? 3 A. Correct. 4 Q. Then you have the opinion that asbestos 5 and fibrous talc cause ovarian cancer. 6 Again, those are opinions that you've 7 formed after being retained in the litigation, 8 correct? 9 A. Correct. 10 Q. And then continuing on to Number 2, the 11 opinion that you've formed concerning heavy metals, 12 is that an opinion that you formed after being 13 retained in the litigation? 14 A. Correct. 15 Q. With respect to -- and the same is true 16 with fragrances, is that an opinion that you formed 17 after being retained in the litigation? 18 A. Correct. 19 Q. And Item Number 3, you express opinions 20 concerning inflammation. 21 Is that a fair paraphrasing of 22 Number 3? 23 MS. O'DELL: Objection to form. 24 A. I don't think those are opinions. I think</p>	<p>1 contain asbestos, what is the credible evidence that 2 you rely upon? 3 A. The paper of Blount in 1991 and the report 4 of Dr. Longo and the other doctor with him whose 5 name I forgot. It starts with an R, I think. 6 MS. O'DELL: I think you mean Rigler. 7 THE WITNESS: That's it. Starts with 8 an R. 9 Q. (BY MR. JAMES) Are those the litigation 10 reports in litigation testimony that we previously 11 discussed? 12 A. Yes, sir. 13 Q. Is there any other evidence that you 14 consider -- that you have considered that supports 15 your opinion that there's, quote, "credible 16 evidence" of asbestos in those products? 17 MS. O'DELL: Object to the form. 18 A. I can't remember any other evidence or 19 references. 20 Q. (BY MR. JAMES) You cite some articles on 21 page 18 of your report? 22 A. Oh, yes. 23 Q. Do you see where I am, Doctor? 24 A. Yes.</p>

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<p>1 Q. And you cite a number of articles there.</p> <p>2 Do you see where I'm looking in the</p> <p>3 first paragraph?</p> <p>4 A. (Examined exhibit.) Yes.</p> <p>5 Q. Okay. In that -- the first paragraph in</p> <p>6 that section?</p> <p>7 A. Yes.</p> <p>8 MS. O'DELL: And we're -- just for</p> <p>9 purposes, we're at page 18?</p> <p>10 MR. JAMES: Correct.</p> <p>11 THE WITNESS: Yeah. We're talking</p> <p>12 about the first sentence.</p> <p>13 MS. O'DELL: Okay.</p> <p>14 Q. (BY MR. JAMES) How did you obtain those</p> <p>15 articles?</p> <p>16 A. Those articles were provided for me as</p> <p>17 reference materials by the plaintiffs' attorneys.</p> <p>18 Q. Do any of those articles pertain to</p> <p>19 Johnson &amp; Johnson products?</p> <p>20 A. Blount disclosed in her deposition that it</p> <p>21 was Johnson &amp; Johnson Baby Powder.</p> <p>22 Q. And I'm -- just to be clear, I'm asking</p> <p>23 about the articles that you've cited in the first</p> <p>24 paragraph in the asbestos section on page 18.</p>	<p>1 reports provided to review.</p> <p>2 Q. (BY MR. JAMES) And those were the reports</p> <p>3 provided to you by plaintiffs' counsel?</p> <p>4 A. Yes.</p> <p>5 Q. And you also cited a number of articles</p> <p>6 that you just testified were provided to you by</p> <p>7 plaintiffs' counsel?</p> <p>8 MS. O'DELL: Object to the form.</p> <p>9 A. Yes.</p> <p>10 Q. (BY MR. JAMES) Did you find any articles</p> <p>11 through your searches that contradicted the</p> <p>12 information provided to you by plaintiffs' counsel?</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 A. Yes.</p> <p>15 Q. (BY MR. JAMES) Where are those articles</p> <p>16 cited in your report?</p> <p>17 A. I don't think I have cited them in my</p> <p>18 report.</p> <p>19 Q. You found articles that contradict the</p> <p>20 allegation that asbestos is a contaminant in talcum</p> <p>21 powder products, correct?</p> <p>22 MS. O'DELL: Object to the form.</p> <p>23 A. It's not a contradiction. The absence of</p> <p>24 something does not contradict the presence of</p>
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<p>1 A. Blount's one of those articles -- well,</p> <p>2 her article -- the deposition is not the paper.</p> <p>3 You're right. Sorry.</p> <p>4 Q. No, that's fine.</p> <p>5 A. I don't know that any of those were</p> <p>6 Johnson &amp; Johnson Baby Powder.</p> <p>7 MS. O'DELL: Just to be -- if you're</p> <p>8 referring to -- when you say "those," it's not clear</p> <p>9 on the record, so if there's something specific --</p> <p>10 you don't have to go back, but just be -- be</p> <p>11 cognizant of that.</p> <p>12 Q. (BY MR. JAMES) What level of review did</p> <p>13 you undertake to collect literature on the topic of</p> <p>14 the alleged presence of asbestos in talcum powder</p> <p>15 products?</p> <p>16 MS. O'DELL: Object to the form.</p> <p>17 A. (Examined exhibit.)</p> <p>18 MS. O'DELL: If you understand the</p> <p>19 question.</p> <p>20 THE WITNESS: I understand the</p> <p>21 question.</p> <p>22 A. I mean, I remember Googling that question</p> <p>23 and getting into a lot of craziness on the internet</p> <p>24 that I didn't want to be in. I relied on the</p>	<p>1 something.</p> <p>2 Do you understand?</p> <p>3 Like in Longo's report, he found</p> <p>4 asbestos in 63 percent of his samples. He did not</p> <p>5 find asbestos in 34 percent of his samples. The</p> <p>6 fact that he didn't find it in 34 percent does not</p> <p>7 mean he didn't find it in 66.</p> <p>8 Asbestos is a carcinogen and its</p> <p>9 significance in risk to life is when you find it.</p> <p>10 In the FDA report that did not find</p> <p>11 asbestos in Johnson's Baby Powder, Shower to Shower,</p> <p>12 and in multiple samples from suppliers of ore -- I</p> <p>13 mean, that's great that they didn't find it, but it</p> <p>14 doesn't mean it's not detectable. And I can't</p> <p>15 explain in terms of being an expert in technique to</p> <p>16 understand why some people found it and some people</p> <p>17 didn't find it.</p> <p>18 Does that make sense to you?</p> <p>19 Q. (BY MR. JAMES) I think you answered a</p> <p>20 question that I didn't ask, so let me rephrase.</p> <p>21 A. I'm sorry.</p> <p>22 Q. In searching for literature about the</p> <p>23 alleged presence of asbestos in cosmetic talc, did</p> <p>24 you find any articles -- published articles that</p>

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<p>1 reach the conclusion that there was no such 2 contamination? 3 MS. O'DELL: Object to the form. 4 A. I can't remember any. 5 Q. (BY MR. JAMES) If you had found those, 6 would you have discussed those in your report? 7 A. Probably. I mean, I want to be 8 comprehensive. 9 Q. And so if there is a body of literature 10 out there that you didn't discuss in your report, 11 then you would agree that your analysis of the issue 12 was not comprehensive, correct? 13 MS. O'DELL: Excuse me. Object to the 14 form; misstates her testimony. 15 A. If I missed it, I shouldn't have. 16 Q. (BY MR. JAMES) And, Dr. Smith, you did 17 just mention the FDA testing of talc for the 18 presence of asbestos, correct? 19 A. Yes. 20 Q. And have you reviewed that testing? 21 A. I've reviewed that report. 22 Q. The FDA's report? 23 A. Yes. 24 Q. Did you discuss it at all in your</p>	<p>1 question? 2 MR. JAMES: The findings in Exhibit 3 Number 7. 4 MS. O'DELL: Object to the form. 5 A. Their -- I -- they said, "No asbestos 6 detected." 7 I can -- I don't know enough about 8 testing to disagree with them, but I don't know 9 what -- I mean, does "none" mean zero or does "none" 10 mean below some level? 11 I do know that their technique -- I 12 know enough to know that it's a good means of 13 finding asbestos by, you know, polarized light 14 microscopy followed by TEM, that that's a good 15 technique. 16 I don't understand why theirs are so 17 different from the other, and I don't have the 18 expertise to go any further than that. 19 Q. (BY MR. JAMES) With respect to whether 20 there is asbestos in the cosmetic talc products or 21 there isn't, is it fair to say that you would defer 22 to others? 23 A. Yes. 24 MS. O'DELL: Object to the form.</p>
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<p>1 litigation report? 2 A. No. 3 Q. And why is that? 4 A. I explained that. Negative isn't as 5 significant as positive. 6 Q. Is that because the positive testing 7 results supports your litigation opinion; the 8 negative testing results do not? 9 MS. O'DELL: Object to the form. 10 A. No. It's because the positive testing is 11 a threat to human life. 12 Q. (BY MR. JAMES) So you have seen -- I'm 13 gonna mark as Exhibit Number 7 the 2007 -- excuse 14 me, the 2010 FDA testing on cosmetic talc. 15 A. Yes. 16 (Deposition Exhibit 7 marked for 17 identification.) 18 Q. (BY MR. JAMES) Is that a printout of the 19 testing information you have reviewed, Dr. Smith? 20 A. That is identical to what I have reviewed. 21 Q. Okay. Do you have any reason to disagree 22 with the FDA's findings here in this Exhibit 7? 23 MS. O'DELL: Object to the form to the 24 degree -- what findings are you referring to in your</p>	<p>1 Q. (BY MR. JAMES) And do you consider 2 yourself to be an expert in mineral classification? 3 A. Absolutely not. 4 Q. What about an expert in mineralogy? 5 A. Absolutely not. 6 Q. But you understand the FDA's testing was 7 performed by an independent lab? 8 A. Yes, they said that. 9 Q. And that's contrasted, which you 10 understand that Longo's testing is done by a paid 11 litigation expert, correct? 12 MS. O'DELL: Object to the form. 13 A. I'm kind of thinking they probably paid 14 the lab they sent it to too. I mean, shouldn't 15 they? 16 Q. (BY MR. JAMES) And who's -- who is 17 "they"? 18 A. The FDA paid the AMA Analytical Services. 19 Q. Okay. Do you have any understanding of 20 how the lab results by the FDA were obtained or paid 21 for? 22 A. No. 23 Q. Do you have an understanding of -- did you 24 know that the FDA's testing was performed outside</p>

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<p>1 the context of litigation?</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 A. I hadn't thought of it, but I would not</p> <p>4 think it's about litigation.</p> <p>5 Q. (BY MR. JAMES) And if we looked at the</p> <p>6 front page of Exhibit Number 7, which I've handed</p> <p>7 you, have you reviewed the text of this exhibit</p> <p>8 before today?</p> <p>9 A. This whole -- yes.</p> <p>10 Q. Okay.</p> <p>11 MS. O'DELL: And if you need to</p> <p>12 look --</p> <p>13 Q. (BY MR. JAMES) And do you understand that</p> <p>14 this exhibit --</p> <p>15 MS. O'DELL: Excuse me. Excuse me.</p> <p>16 If you -- and if you need to refresh</p> <p>17 yourself on any part of the text, Doctor, feel free</p> <p>18 to do that as he's asking you questions.</p> <p>19 THE WITNESS: Okay.</p> <p>20 MR. JAMES: Absolutely. Certainly.</p> <p>21 Q. (BY MR. JAMES) If you turn to the second</p> <p>22 page of the exhibit, do you see the section that's</p> <p>23 titled "How FDA followed up on the latest reports"?</p> <p>24 A. Yes.</p>	<p>1 Q. Have you looked at those?</p> <p>2 A. No, I have not.</p> <p>3 Q. Are you aware that Johnson &amp; Johnson</p> <p>4 manufacturers its products in accordance with United</p> <p>5 States Pharmacopeia Convention?</p> <p>6 MS. O'DELL: Objection to form.</p> <p>7 A. I did not know that specifically.</p> <p>8 Q. (BY MR. JAMES) Have heard of that</p> <p>9 organization before?</p> <p>10 A. Yes, I have.</p> <p>11 Q. Do you consider that to be a respected</p> <p>12 organization?</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 A. Yes.</p> <p>15 Q. (BY MR. JAMES) Did you know that there</p> <p>16 have been thousands upon thousands of testing</p> <p>17 documents produced in this litigation?</p> <p>18 MS. O'DELL: Object to the form.</p> <p>19 A. I --</p> <p>20 MS. O'DELL: Don't speculate. If</p> <p>21 you -- if you --</p> <p>22 THE WITNESS: I --</p> <p>23 MR. JAMES: I'm asking her if she</p> <p>24 knew.</p>
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<p>1 Q. Okay. And you see it says, quote,</p> <p>2 "Because safety questions about the possible</p> <p>3 presence of asbestos in talc are raised</p> <p>4 periodically, the FDA decided to conduct an</p> <p>5 exploratory survey of currently marketed</p> <p>6 cosmetic-grade raw material talc," closed quote.</p> <p>7 Do you see where I read?</p> <p>8 A. Yes.</p> <p>9 Q. And there's no discussion there that the</p> <p>10 testing was done at the behest of litigation, is</p> <p>11 there?</p> <p>12 A. No.</p> <p>13 Q. And did you know that the talcum products</p> <p>14 tested by the FDA in this document were Johnson &amp;</p> <p>15 Johnson products?</p> <p>16 MS. O'DELL: Object to the form.</p> <p>17 A. I think it says Johnson's Baby Powder and</p> <p>18 Shower to Shower on there, and I know those are J&amp;J</p> <p>19 products.</p> <p>20 Q. (BY MR. JAMES) Do you have any personal</p> <p>21 knowledge concerning the specifications that are</p> <p>22 used by Johnson &amp; Johnson with respect to its</p> <p>23 cosmetic talcum powder products?</p> <p>24 A. I do not know them.</p>	<p>1 THE WITNESS: -- was going to say I</p> <p>2 didn't know.</p> <p>3 MS. O'DELL: Okay. Good. I didn't</p> <p>4 hear what your answer was. Sorry.</p> <p>5 THE WITNESS: Okay.</p> <p>6 MS. O'DELL: I didn't -- I talked over</p> <p>7 you. I apologize.</p> <p>8 THE WITNESS: That's okay.</p> <p>9 Q. (BY MR. JAMES) So the -- just so that the</p> <p>10 exchange is clear, Doctor, did you know that there</p> <p>11 have been thousands upon thousands of testing</p> <p>12 documents produced in this litigation?</p> <p>13 A. I did not.</p> <p>14 Q. Did you know that those testing documents</p> <p>15 include testing documents performed by third-party</p> <p>16 labs?</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 A. I did not.</p> <p>19 Q. (BY MR. JAMES) Did you review a 2014</p> <p>20 letter by the FDA in the course of forming your</p> <p>21 opinions in this case?</p> <p>22 A. Could you show me that letter?</p> <p>23 Q. Absolutely.</p> <p>24 A. See if I recognize it.</p>

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<p style="text-align: right;">Page 106</p> <p>1 MR. JAMES: I'm gonna mark as Exhibit 2 Number 8 -- it's the 2014 FDA letter denying the 3 Citizen Petitions. 4 (Deposition Exhibit 8 marked for 5 identification.) 6 A. (Examined exhibit.) Yes, sir, I have seen 7 this letter. 8 Q. (BY MR. JAMES) Did you consider this 9 letter informative -- to be informative of your 10 opinions? 11 MS. O'DELL: Object to the form. 12 A. I read this report, and it went into a 13 total database. 14 Q. (BY MR. JAMES) And does that mean your 15 total set of materials that you considered? 16 A. Yes, it's my brain. 17 Q. Do you understand that in this letter the 18 FDA also commented on the allegation that asbestos 19 contaminates cosmetic talc products? 20 A. Yes. 21 Q. And did you -- do you recall seeing the 22 FDA's conclusion in this letter about that 23 allegation? 24 MS. O'DELL: Feel free to refresh</p>	<p style="text-align: right;">Page 108</p> <p>1 asbestos. 2 Q. (BY MR. JAMES) And my -- the question 3 that I posed before Ms. O'Dell made her speaking 4 objection was that do you have any reason to 5 disagree with the FDA's statements in this letter 6 about the allegation that asbestos contaminates talc 7 products? 8 MS. O'DELL: Object to the form; 9 misstates the document. 10 A. (Examined realtime screen.) 11 I share the FDA's concern that they 12 make a blanket statement with testing only some of 13 the suppliers and a limited number of products and a 14 limited number of samples of those products, so I -- 15 I understand they -- how they base their conclusion. 16 I might have or would have suggested additional 17 studies. 18 Q. (BY MR. JAMES) And you understand -- 19 again, we've discussed this already, but of the 20 products tested, those products included Johnson &amp; 21 Johnson products. 22 Did you know that? 23 A. Yes. I -- they had a single sample of 24 Johnson &amp; Johnson powder from the DC area.</p>
<p style="text-align: right;">Page 107</p> <p>1 yourself about the document, Dr. Smith. 2 A. (Examined exhibit.) My understanding was 3 their conclusions was that they were not going to 4 issue a warning on products, nor were they going to 5 allow a hearing for further discussion. 6 Q. (BY MR. JAMES) And you understand that in 7 this 2014 letter the FDA referred back to its 2010 8 testing for presence of asbestos, correct? 9 A. Correct. 10 Q. Do you have any reason to disagree with 11 the FDA's statements in this letter about the 12 allegation that asbestos contaminates talc products? 13 MS. O'DELL: Object to the form. 14 I think Dr. Smith misunderstood your 15 prior question. Counsel, I think you sort of missed 16 each other. 17 But your context of this question is 18 asbestos, not the overall finding of the letter, but 19 asbestos itself? 20 Q. (BY MR. JAMES) Dr. Smith, can you answer 21 my question? 22 A. I may have to read it again. 23 (Examined realtime screen.) Yes, they 24 did refer back to the 2010 testing for presence of</p>	<p style="text-align: right;">Page 109</p> <p>1 Q. Do you understand that the supplier of the 2 talc that's used in Johnson &amp; Johnson products also 3 submitted samples? 4 A. Yes, I did. 5 Q. Do you have any opinions about the amount 6 of exposure to asbestos that you believe would be 7 imparted upon a user of Johnson &amp; Johnson talc 8 products? 9 MS. O'DELL: Object to the form; vague 10 as to time and duration. 11 A. No. 12 Q. (BY MR. JAMES) And do you have any 13 opinions about the alleged contamination on a 14 fiber-per-bottle basis? 15 MS. O'DELL: Object to the form. 16 A. No. 17 Q. (BY MR. JAMES) Do you have an opinion as 18 to when you believe J&amp;J talc powder products were 19 contaminated with asbestos and on the market? 20 MS. O'DELL: Object to the form. 21 A. Yes. 22 Q. (BY MR. JAMES) What is that opinion? 23 A. My opinion is that contamination occurs at 24 the mine and persists through the processing all the</p>

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<p>1 way to market.</p> <p>2 Q. Okay. I think you misunderstood my</p> <p>3 question or maybe I asked a bad question.</p> <p>4 But do you have any opinion about</p> <p>5 when, for what duration or period of years,</p> <p>6 Johnson &amp; Johnson talc products were on the market</p> <p>7 and were allegedly contaminated with asbestos?</p> <p>8 MS. O'DELL: Object to the form.</p> <p>9 A. Dr. Longo has tested samples from the '70s</p> <p>10 to 2000 with the presence of a -- presence of</p> <p>11 asbestos.</p> <p>12 Q. (BY MR. JAMES) And, again, you're</p> <p>13 referring back to the Longo litigation testing that</p> <p>14 we've talked about at length --</p> <p>15 A. Yes.</p> <p>16 Q. -- this morning, correct?</p> <p>17 A. Yes.</p> <p>18 MS. O'DELL: Objection to form.</p> <p>19 Excuse me. Object to the form.</p> <p>20 Q. (BY MR. JAMES) Do you have any opinion</p> <p>21 about -- well, strike that.</p> <p>22 With respect to your opinion that</p> <p>23 asbestos is a cause of ovarian cancer, how did you</p> <p>24 go about searching for the materials that you</p>	<p>1 A. Yes.</p> <p>2 Q. Okay. Did you review any other studies</p> <p>3 examining the purported relationship between</p> <p>4 asbestos and ovarian cancer?</p> <p>5 A. Not that I remember.</p> <p>6 Q. Does this report reflect your complete</p> <p>7 analysis of those studies?</p> <p>8 MS. O'DELL: Object to the form.</p> <p>9 Q. (BY MR. JAMES) And how they relate to</p> <p>10 your opinions in this case?</p> <p>11 MS. O'DELL: Objection to form.</p> <p>12 A. Yes. I believe so.</p> <p>13 Q. (BY MR. JAMES) Do you recall looking at</p> <p>14 the Reid study? Do you -- sitting here today, do</p> <p>15 you recall the Reid study?</p> <p>16 A. That's my favorite one. May I see it.</p> <p>17 Q. Sure.</p> <p>18 MS. O'DELL: Yes. Please.</p> <p>19 Q. (BY MR. JAMES) Did you say -- I'm sorry.</p> <p>20 Did you say the Reid study was your</p> <p>21 favorite study?</p> <p>22 A. Yes.</p> <p>23 MS. O'DELL: On this topic, Doctor.</p> <p>24 THE WITNESS: In my life, no. It is</p>
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<p>1 reviewed to inform that opinion?</p> <p>2 A. I reviewed articles that were listed in</p> <p>3 IARC 100C and --</p> <p>4 Q. And the -- oh, I'm sorry, Doctor.</p> <p>5 A. -- then PubMed research as well.</p> <p>6 THE COURT REPORTER: What did you say?</p> <p>7 THE WITNESS: PubMed, P-u-b-M-e-d</p> <p>8 Q. And on page 18 through 19, Doctor, is,</p> <p>9 again, your section on asbestos, correct?</p> <p>10 A. Um-hum. Um-hum.</p> <p>11 Q. And in that section, Doctor, you refer to</p> <p>12 the IARC, which you just mentioned, correct?</p> <p>13 A. Correct.</p> <p>14 Q. And then you cite five, what you refer to</p> <p>15 as, quote, "heavy occupational exposure," close</p> <p>16 quote, studies, correct?</p> <p>17 A. Correct.</p> <p>18 Q. And below that you also discuss the</p> <p>19 Camargo study; is that right?</p> <p>20 A. Correct.</p> <p>21 Q. And then if you turn the page, you refer</p> <p>22 in a single sentence to a Reid study, correct?</p> <p>23 A. Correct.</p> <p>24 Q. Did you review all of those studies?</p>	<p>1 not my favorite study in my life, but . . .</p> <p>2 MR. JAMES: Okay. I'm gonna mark the</p> <p>3 Reid study as Exhibit Number 9.</p> <p>4 (Deposition Exhibit 9 marked for</p> <p>5 identification.)</p> <p>6 A. (Examined exhibit.)</p> <p>7 MR. JAMES: Oh, thank you.</p> <p>8 Q. (BY MR. JAMES) Have you had a chance to</p> <p>9 refresh your recollection of the study, Doctor?</p> <p>10 A. Um-hum. Um-hum.</p> <p>11 Q. And why is this your favorite study?</p> <p>12 A. As a pathology review discriminating</p> <p>13 mesothelioma from epithelial ovarian cancer.</p> <p>14 Q. And you don't have any -- strike that.</p> <p>15 The discussion that you've included in</p> <p>16 your report as to Reid is that single sentence,</p> <p>17 correct?</p> <p>18 A. Yes.</p> <p>19 Q. Do you --</p> <p>20 A. And it's a meta-analysis.</p> <p>21 Q. Do you agree with the statements in the</p> <p>22 Reid study about misclassification?</p> <p>23 A. Exactly what statements, please?</p> <p>24 Q. Sure.</p>

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<p style="text-align: right;">Page 114</p> <p>1 So if you look towards the Conclusion</p> <p>2 section that's on the second to last page of the</p> <p>3 article.</p> <p>4 A. (Complied.) Thank you.</p> <p>5 Q. And if you look at the Conclusion section,</p> <p>6 I'll just read the first couple sentences.</p> <p>7 The article says, quote, "Taken</p> <p>8 without further analysis, women thought to have</p> <p>9 ovarian cancer had an increased rate in the</p> <p>10 meta-analysis if reporting having been exposed to</p> <p>11 asbestos, compared with reference populations."</p> <p>12 (Paraphrasing.) However, this finding may result</p> <p>13 from the methods used to identify the ovarian cancer</p> <p>14 cases, close quote.</p> <p>15 A. Yes.</p> <p>16 Q. Do you agree with the concern expressed in</p> <p>17 Reid about the disease misclassification?</p> <p>18 A. I do.</p> <p>19 Q. And then if you scan further down in that</p> <p>20 paragraph of the article, Doctor, you see, you know,</p> <p>21 about halfway to three-quarters of the way down,</p> <p>22 there's a sentence that starts with the word</p> <p>23 "However."</p> <p>24 It says, quote, "However, the authors</p>	<p style="text-align: right;">Page 116</p> <p>1 A. I think the weight of the evidence falls</p> <p>2 with the IARC even though they're meta-analysis</p> <p>3 crossed -- their -- no, their meta-analysis didn't.</p> <p>4 The overall -- I mean, their findings</p> <p>5 have a risk of 1.75 with confidence intervals of</p> <p>6 1.45 to 2.10.</p> <p>7 So, again, she has a positive study</p> <p>8 with pathology review, and then she says the IARC is</p> <p>9 premature. I don't understand her conclusion.</p> <p>10 Q. Do you understand that, again, her --</p> <p>11 her -- the cautions expressed in this last</p> <p>12 paragraph, some of those cautions arise from the</p> <p>13 concerns about disease in this classification.</p> <p>14 Do you understand that?</p> <p>15 MS. O'DELL: Object to the form.</p> <p>16 A. Yes.</p> <p>17 Q. (BY MR. JAMES) And do you agree with</p> <p>18 those concerns?</p> <p>19 MS. O'DELL: Object to the form.</p> <p>20 A. I think it is very difficult to</p> <p>21 discriminate mesothelioma from epithelial ovarian</p> <p>22 cancer sometimes.</p> <p>23 Q. (BY MR. JAMES) And I received word that</p> <p>24 the tape needs to be changed so --</p>
<p style="text-align: right;">Page 115</p> <p>1 of this article suggest that the IARC decision to</p> <p>2 determine asbestos exposure as a cause of ovarian</p> <p>3 cancer was premature and not wholly supported by the</p> <p>4 evidence" --</p> <p>5 A. Are you on the back page?</p> <p>6 Q. -- close quote.</p> <p>7 Yes. On the same paragraph that I was</p> <p>8 reading with you earlier. It's the Conclusion</p> <p>9 paragraph.</p> <p>10 A. Where it says "Discussions"? Oh, no.</p> <p>11 Q. I'm on page --</p> <p>12 A. Oh, I'm --</p> <p>13 Q. -- 1294.</p> <p>14 A. Okay. I've caught up with you now.</p> <p>15 Sorry. (Examined exhibit.)</p> <p>16 Q. And I was reading a sent- -- a sentence</p> <p>17 that started with the word "However."</p> <p>18 A. All right. Um-hum. (Examined exhibit.)</p> <p>19 Q. Do you agree with the Reid authors that</p> <p>20 the determination of IARC was premature?</p> <p>21 A. No, I do not.</p> <p>22 Q. Do you agree with the authors of the Reid</p> <p>23 paper that the IARC conclusion was not wholly</p> <p>24 supported by the evidence?</p>	<p style="text-align: right;">Page 117</p> <p>1 A. Okay.</p> <p>2 Q. -- we'll take a short break.</p> <p>3 A. Okay.</p> <p>4 THE VIDEOGRAPHER: Going off the</p> <p>5 record. The time is 11:39 a.m.</p> <p>6 (A recess was taken from 11:39 a.m.</p> <p>7 to 11:55 a.m.)</p> <p>8 THE VIDEOGRAPHER: This marks the</p> <p>9 beginning of Disk 2. Back on the record. The time</p> <p>10 is 11:55 a.m.</p> <p>11 Q. (BY MR. JAMES) Dr. Smith, we are</p> <p>12 continuing our discussion of your opinion on</p> <p>13 asbestos as causes of ovarian cancer. Okay?</p> <p>14 A. Correct.</p> <p>15 Q. Did you consider any weaknesses or</p> <p>16 limitations in the body of the literature that you</p> <p>17 reviewed concerning the link between asbestos and</p> <p>18 ovarian cancer?</p> <p>19 A. Could you be more specific?</p> <p>20 Q. Certainly in evaluating medical literature</p> <p>21 you would agree that one thing for you to consider</p> <p>22 is whether the study has any limitations, correct?</p> <p>23 A. Correct.</p> <p>24 Q. And so my question, which is open-ended,</p>

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<p>1 is whether, in looking at the set of literature that</p> <p>2 you looked at on asbestos and ovarian cancer, if you</p> <p>3 found any limitations to that set of literature?</p> <p>4 MS. O'DELL: Objection; vague.</p> <p>5 A. I've considered whether they're single</p> <p>6 site studies, occupational exposure -- exposure</p> <p>7 versus people who wash the clothes of workers or</p> <p>8 nonenvironmental exposure as opposed to</p> <p>9 occupational, those things.</p> <p>10 Q. (BY MR. JAMES) And --</p> <p>11 A. And --</p> <p>12 Q. -- so let's start --</p> <p>13 MS. O'DELL: I'm sorry. Were you</p> <p>14 finished, Dr. Smith? If you --</p> <p>15 THE WITNESS: I have.</p> <p>16 MS. O'DELL: Okay.</p> <p>17 Q. (BY MR. JAMES) Let's -- so you just</p> <p>18 identified one limitation as -- let me -- let me</p> <p>19 rephrase this.</p> <p>20 Would you agree that one limitation of</p> <p>21 the set of literature that you reviewed was that --</p> <p>22 (Phone interruption.)</p> <p>23 THE WITNESS: What is that?</p> <p>24 MR. JAMES: Just a second. Let's go</p>	<p>1 that's okay. I'll try to talk quicker, and you can</p> <p>2 try to anticipate my questions less.</p> <p>3 MS. O'DELL: Well, and if you would --</p> <p>4 yes, and give me a moment just to respond --</p> <p>5 THE WITNESS: Sorry.</p> <p>6 MS. O'DELL: -- respond with an</p> <p>7 objection if I need to.</p> <p>8 THE WITNESS: I'll get better.</p> <p>9 MS. O'DELL: Thank you. You're doing</p> <p>10 great.</p> <p>11 Q. (BY MR. JAMES) You agree that long-term</p> <p>12 exposure to asbestos in an indust- -- in an</p> <p>13 industrial environment is different than the</p> <p>14 allegation that a person's exposed to</p> <p>15 asbestos-contaminated talc products --</p> <p>16 MS. O'DELL: Object --</p> <p>17 Q. (BY MR. JAMES) -- correct?</p> <p>18 MS. O'DELL: Object to the form.</p> <p>19 A. If you are talking about difference in</p> <p>20 terms of dosage and -- and amount of exposure, then</p> <p>21 I would say there's probably a difference.</p> <p>22 If you would suggest that the</p> <p>23 mechanism of carcinogenesis is different, then I</p> <p>24 would say no, it's probably the same.</p>
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<p>1 off.</p> <p>2 THE VIDEOGRAPHER: Going off the</p> <p>3 record. The time is 11:57.</p> <p>4 (A recess was taken from 11:57 a.m.</p> <p>5 to 11:58 a.m.)</p> <p>6 THE VIDEOGRAPHER: Back on the record.</p> <p>7 The time is 11:58 a.m.</p> <p>8 Q. (BY MR. JAMES) Dr. Smith, would you agree</p> <p>9 that one limitation to this set of literature that</p> <p>10 you reviewed is that the literature pertains to</p> <p>11 occupational exposures?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A. It contains occupational exposure and, I</p> <p>14 mean, the meta-analysis of Reid, for example. It</p> <p>15 contains both.</p> <p>16 Q. (BY MR. JAMES) Do you -- would you agree</p> <p>17 that for the studies that pertain to occupational</p> <p>18 exposure that you've reviewed that's one limitation</p> <p>19 to those studies in applying them to the --</p> <p>20 A. Nonoccupational people, yes.</p> <p>21 Q. Thank you. And the doctor finished my</p> <p>22 question.</p> <p>23 A. Sorry.</p> <p>24 Q. And I -- we understood each other, so</p>	<p>1 Q. (BY MR. JAMES) And you agree that some of</p> <p>2 the studies that the IARC looked at were in the</p> <p>3 occupational context, correct?</p> <p>4 A. Correct.</p> <p>5 Q. And, in fact, the IARC's conclusion on</p> <p>6 causation was heavily weighted on the occupational</p> <p>7 studies, correct?</p> <p>8 MS. O'DELL: Object to the form.</p> <p>9 A. I'd have to look at the IARC study again</p> <p>10 to see how they stated it. And I could do that, if</p> <p>11 you want me to.</p> <p>12 Q. (BY MR. JAMES) Do you recall that when</p> <p>13 the IARC looked at the nonoccupational studies the</p> <p>14 association that they found there was not</p> <p>15 statistically significant?</p> <p>16 MS. O'DELL: Objection to the form.</p> <p>17 A. I don't recall that.</p> <p>18 Q. (BY MR. JAMES) If that's the case, do you</p> <p>19 believe that's important?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A. I'd like to look at the paper if you'd</p> <p>22 let -- if you'd let me.</p> <p>23 Q. (BY MR. JAMES) Sure.</p> <p>24 THE WITNESS: Am I allowed to see it?</p>

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<p>1 Q. (BY MR. JAMES) That's fine. That's fine. 2 Let's talk about -- talk about -- 3 we'll talk about the paper more -- more specifically 4 in just a second. 5 A. Okay. 6 Q. If I can continue the line of questions on 7 the limitations. 8 A. Okay. 9 Q. So we've talked about occupational -- 10 MS. O'DELL: Excuse me. 11 Q. (BY MR. JAMES) -- being one limitation, 12 correct? 13 MS. O'DELL: Excuse me. Doctor -- 14 MR. JAMES: Leigh, there's not a 15 question pending. 16 MS. O'DELL: She's asked to look at 17 IARC 100C, and if the witness has asked to look at 18 the document, I'm going to put it in front of her. 19 Give me just a second. 20 THE WITNESS: It's the second IA. 21 It's the first thing in the second IA. 22 MS. O'DELL: (Handed binder to 23 witness.) 24 THE WITNESS: Thank you.</p>	<p>1 Q. (BY MR. JAMES) So I'm going to hand 2 you -- I think we're all on the same page now. I'm 3 gonna hand you also a copy with some excerpts from 4 100C. Okay? 5 A. Okay. 6 Q. And I'm gonna mark it as Exhibit 7 Number 10. 8 (Deposition Exhibit 10 marked for 9 identification.) 10 MS. O'DELL: Thank you. Feel free to 11 refer to the whole monograph if you'd like, 12 Doctor -- Dr. Smith. 13 THE WITNESS: Okay. 14 A. I turned right to it. 15 Q. (BY MR. JAMES) Okay. Doctor, if you can 16 look at page 256 -- 17 A. Yeah. 18 Q. -- of either the exhibit that I handed you 19 with the excerpts or you're welcome to look at the 20 larger monograph as well. 21 A. I'm there. 22 Q. And if you look at the right-hand column, 23 it's the first full paragraph in that column. It 24 starts with "The Working Group."</p>
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<p>1 A. (Examined binder.) 2 Q. (BY MR. JAMES) Okay. Dr. Smith, your 3 counsel has handed you a copy of the IARC talc 4 monograph, correct? 5 A. Correct. 6 Q. Okay. And I'm gonna mark as Exhibit 7 Number 10 -- 8 MS. O'DELL: I'm sorry. You said the 9 talc monograph. I handed her 100C. Not -- 10 MR. JAMES: Oh. Thank you. 11 BY MS. O'DELL: Not monograph. 12 MR. JAMES: You're right. 13 BY MS. O'DELL: 193. 14 MR. JAMES: You're right. You're 15 right. Thank you. 16 Q. (BY MR. JAMES) So I am going to -- I'll 17 refer to it commonly as the asbestos monograph 18 for -- for a simple shorthand. 19 So your counsel has handed you a copy 20 of the asbestos monograph 100C and -- 21 MS. O'DELL: Which -- which discusses 22 talc, so I don't want to be misleading. 23 THE WITNESS: No, 193 discusses talc. 24 100C discusses asbestos.</p>	<p>1 Do you see where I'm reading? 2 A. Um-hum. Um-hum. Yes. 3 Q. And if you look down at the bottom half of 4 that paragraph, the IARC Monograph states, quote, 5 "The conclusion received additional support from 6 studies showing that women and girls with 7 environmental, but not occupational exposure to 8 asbestos had positive, though non-significant, 9 increases in both ovarian cancer incidence and 10 mortality," close quote. 11 Do you see where I read that? 12 A. Yes. 13 Q. And did I read that correctly? 14 A. Yes. 15 Q. So here the IARC is commenting that in the 16 nonoccupational studies the association is not 17 statistically significant, correct? 18 MS. O'DELL: Object to the form. 19 A. In the articles, they cited, IARC -- this 20 started in 2009 and was published in 2012, and I do 21 not believe they had the 2011 meta-analysis by Reid 22 in this. They cite Reid 2008 and 2009, but not the 23 meta-analysis. So what they have, they're making 24 their conclusions there.</p>

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<p>1 Q. (BY MR. JAMES) Right.</p> <p>2 A. I think this adds to it.</p> <p>3 Q. The Reid paper?</p> <p>4 A. The 2011 Reid paper.</p> <p>5 Q. And the 2011 Reid paper, again, is the</p> <p>6 paper where the authors conclude that the IARC's</p> <p>7 finding with respect to asbestos and ovarian cancer</p> <p>8 is -- may be premature, correct?</p> <p>9 A. I disa- --</p> <p>10 MS. O'DELL: Object to the form.</p> <p>11 A. Yes. You are correct that that is their</p> <p>12 conclusion. I disagree with their conclusion. It</p> <p>13 is your Exhibit 9.</p> <p>14 Q. (BY MR. JAMES) And so you disagree with</p> <p>15 the conclusions of -- of the paper that you qual- --</p> <p>16 that you categorized as one of your favorites,</p> <p>17 correct?</p> <p>18 MS. O'DELL: Object to the form.</p> <p>19 A. Yes.</p> <p>20 Q. (BY MR. JAMES) And if you look up on the</p> <p>21 same paragraph, Dr. Smith --</p> <p>22 A. Um-hum.</p> <p>23 Q. -- the first sentence of that paragraph</p> <p>24 reads, quote: (Paraphrasing.) The Working Group</p>	<p>1 posed is about the body of literature that you</p> <p>2 reviewed to inform your opinions about asbestos and</p> <p>3 ovarian cancer.</p> <p>4 Are there any other limitations that</p> <p>5 you can identify for us today?</p> <p>6 MS. O'DELL: Objection to form; vague.</p> <p>7 A. I think the IARC -- I forgot how to speak</p> <p>8 English. Sorry.</p> <p>9 The IARC conclusion that asbestos is</p> <p>10 causative in ovarian cancer is expanded by two</p> <p>11 meta-analyses as opposed to these single studies,</p> <p>12 EPI studies, even though they're cohort studies of</p> <p>13 Camargo and Reid.</p> <p>14 Reid doesn't agree with her own</p> <p>15 statistical findings. I don't know why she did</p> <p>16 that.</p> <p>17 Q. (BY MR. JAMES) Well, the Reid authors</p> <p>18 considered the limitations of the body of</p> <p>19 literature, correct?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A. Everyone considers the limitations of the</p> <p>22 body of literature when they write a paper.</p> <p>23 Q. (BY MR. JAMES) Right. So do you -- do</p> <p>24 you think Reid did anything incorrectly in</p>
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<p>1 noted that a causal association between exposure to</p> <p>2 asbestos and cancer of the ovary was clearly</p> <p>3 established, based on five strongly positive</p> <p>4 mort- -- mortality studies of women with heavy</p> <p>5 occupational exposure to asbestos, close quote.</p> <p>6 Do you see that?</p> <p>7 A. Correct.</p> <p>8 Q. So, again, the IARC here is emphasizing</p> <p>9 that the body of literature that supports the IARC's</p> <p>10 finding is the occupational body of literature,</p> <p>11 correct?</p> <p>12 MS. O'DELL: Objection to the form.</p> <p>13 A. Correct.</p> <p>14 Q. (BY MR. JAMES) Are there any other</p> <p>15 limitations that -- that you can think of with</p> <p>16 respect to this set of literature?</p> <p>17 And when I say "set," I refer to the</p> <p>18 literature exploring the relationship between</p> <p>19 asbestos and ovarian cancer.</p> <p>20 A. In IARC --</p> <p>21 MS. O'DELL: Object to the form;</p> <p>22 vague.</p> <p>23 A. -- 100C.</p> <p>24 Q. (BY MR. JAMES) The -- yes. My question</p>	<p>1 evaluating the limitations of the body of</p> <p>2 literature?</p> <p>3 A. I think she made an incorrect conclusion.</p> <p>4 I don't think that necessarily has to do with the</p> <p>5 limitations of the body.</p> <p>6 She has statistically significant</p> <p>7 meta-analytic study even though the strength is low,</p> <p>8 but she -- and then she says -- I disagree with it.</p> <p>9 I don't think it's significant.</p> <p>10 I mean, it's 1.75. What -- I don't --</p> <p>11 I don't understand how she reached her conclusion.</p> <p>12 Q. But you understand she -- the paper notes</p> <p>13 the concern for misclassification, which we've</p> <p>14 already discussed, correct?</p> <p>15 A. Right. But she accounted for that in her</p> <p>16 studies, so I --</p> <p>17 Q. What do you mean by that?</p> <p>18 A. She had a patholo- -- she had pathologic</p> <p>19 review accounted for within here too.</p> <p>20 MS. O'DELL: When you say "here,"</p> <p>21 you're referring to Exhibit 9, the Reid paper?</p> <p>22 THE WITNESS: Yes.</p> <p>23 MS. O'DELL: Okay.</p> <p>24 THE WITNESS: Sorry. I wasn't clear,</p>

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<p style="text-align: right;">Page 130</p> <p>1 and the camera probably can't see it too.</p> <p>2 Q. (BY MR. JAMES) So the authors of the Reid</p> <p>3 paper conclude that disease misclassification may be</p> <p>4 such a problem such that the IARC's conclusion may</p> <p>5 be premature?</p> <p>6 MS. O'DELL: Objection to --</p> <p>7 Q. (BY MR. JAMES) And you're saying that the</p> <p>8 authors --</p> <p>9 MS. O'DELL: Excuse me. Have you</p> <p>10 finished your question? Sorry.</p> <p>11 MR. JAMES: No.</p> <p>12 MS. O'DELL: Okay.</p> <p>13 Q. (BY MR. JAMES) You're saying the author's</p> <p>14 just got it -- got it wrong?</p> <p>15 MS. O'DELL: Object to the form.</p> <p>16 A. I disagree with their conclusion.</p> <p>17 Q. (BY MR. JAMES) So with mis- -- with this</p> <p>18 set of literature we've talked about two limitations</p> <p>19 so far: Misclassification and occupational versus</p> <p>20 nonoccupational, correct?</p> <p>21 A. We've talked about those two things, yes.</p> <p>22 Q. Are there any other limitations to the</p> <p>23 body of literature that you reviewed that you can</p> <p>24 identify today?</p>	<p style="text-align: right;">Page 132</p> <p>1 taking me a minute here, Table 2.</p> <p>2 Small number of cases. When they are</p> <p>3 talking about all cases combining, studying 5,240</p> <p>4 cases, is that a small number?</p> <p>5 Q. (BY MR. JAMES) Do you believe there's --</p> <p>6 one of the limitations to this body of literature is</p> <p>7 the small number of cases?</p> <p>8 A. No. No.</p> <p>9 Q. Do you believe that there are any</p> <p>10 limitations to this literature associated with the</p> <p>11 type of asbestos involved in these studies?</p> <p>12 A. No.</p> <p>13 Q. Are you familiar with the type of asbestos</p> <p>14 involved in these occupational studies?</p> <p>15 A. Each of the studies list types, at least</p> <p>16 some of them do.</p> <p>17 Q. Does that matter to you at all?</p> <p>18 A. Big picture, probably not.</p> <p>19 Q. Okay. So does the type of asbestos at</p> <p>20 issue in the studies looked at by the IARC matter to</p> <p>21 you at all in your opinion that asbestos</p> <p>22 contamination in talc is causative of ovarian</p> <p>23 cancer?</p> <p>24 MS. O'DELL: Objection to form.</p>
<p style="text-align: right;">Page 131</p> <p>1 MS. O'DELL: Object to the form;</p> <p>2 vague.</p> <p>3 A. No.</p> <p>4 MS. O'DELL: Are you limiting that to</p> <p>5 asbestos and ovarian cancer or are you limit -- I</p> <p>6 mean --</p> <p>7 MR. JAMES: Yes. We're talking about</p> <p>8 the subset of literature, which I've said several</p> <p>9 times, pertaining to the allegation that asbestos is</p> <p>10 causative of ovarian cancer. That's what we're</p> <p>11 talking about right now.</p> <p>12 MS. O'DELL: That makes it clear. I</p> <p>13 don't want something taken out of the record later</p> <p>14 and it's not -- it's not clear.</p> <p>15 MR. JAMES: Fair enough.</p> <p>16 A. We've talked about those things. At this</p> <p>17 time, I can think of nothing else.</p> <p>18 Q. (BY MR. JAMES) Do you consider the small</p> <p>19 number of cases to be a limitation to that body of</p> <p>20 literature pertaining to the allegation that</p> <p>21 asbestos is -- is a cause of ovarian cancer?</p> <p>22 MS. O'DELL: Object to the form.</p> <p>23 A. (Examined exhibit.) I'm looking at the</p> <p>24 numbers in the Reid study, and I'm sorry, it's</p>	<p style="text-align: right;">Page 133</p> <p>1 A. I don't remember a breakdown by type in</p> <p>2 the IARC by tremolite or actinolite or -- you know,</p> <p>3 I don't remember that breakdown.</p> <p>4 Q. (BY MR. JAMES) And it's not addressed in</p> <p>5 your report, correct?</p> <p>6 A. It is not addressed in my report.</p> <p>7 Q. To reach your opinion that asbestos is a</p> <p>8 cause of ovarian cancer, what methodology did you</p> <p>9 apply?</p> <p>10 A. The same methodology I applied -- I apply</p> <p>11 every time. I read all the literature that I could</p> <p>12 find. I read it critically. Went through the</p> <p>13 tables, read the footnotes, and made a conclusion,</p> <p>14 as did IARC 100C.</p> <p>15 Q. Is your causation opinion based on IARC?</p> <p>16 A. I think we reached the same conclusion. I</p> <p>17 certainly got a bunch of references from IARC.</p> <p>18 But as I told you, I make my own</p> <p>19 conclusions, even when they disagree with an author</p> <p>20 of a paper. So I'm certainly influenced by their</p> <p>21 conclusion, but I made my conclusion, and I felt</p> <p>22 freedom to disagree if I did.</p> <p>23 Q. Did you read all the studies that IARC</p> <p>24 discussed?</p>

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<p>1 A. Yes.</p> <p>2 Q. Did you read the nonoccupational studies?</p> <p>3 A. I read all of these studies. They are --</p> <p>4 I would have to look at them individually or go to</p> <p>5 details of them.</p> <p>6 Q. Is there a reason why you didn't discuss</p> <p>7 the nonoccupational studies but you did discuss the</p> <p>8 occupational studies?</p> <p>9 MS. O'DELL: Object to the form.</p> <p>10 A. I discussed two meta-analyses that include</p> <p>11 occupational and nonoccupational exposure because,</p> <p>12 as I stated other places in my report, I give</p> <p>13 strength to a meta-analysis above a single either</p> <p>14 occupational or nonoccupational exposure.</p> <p>15 Q. (BY MR. JAMES) And in that section, you</p> <p>16 did cite to the five occupational studies, but you</p> <p>17 actually don't cite to the nonoccupational studies</p> <p>18 in the text of your report.</p> <p>19 And so that's the genesis of my</p> <p>20 question is: Did you actually look at the</p> <p>21 nonoccupational studies?</p> <p>22 MS. O'DELL: Objection to form; asked</p> <p>23 and answered.</p> <p>24 A. If -- if there's a study that's -- that I</p>	<p>1 Q. Is the odds ratio that you just cited, the</p> <p>2 odds ratio, applicable to the occupational studies</p> <p>3 or the nonoccupational studies?</p> <p>4 A. Well, there's an occupational one.</p> <p>5 There's a little bit lower. There tend to be in</p> <p>6 the -- the statistically significant ones tend to be</p> <p>7 a 2.27s, 2.53s, not like -- not like asbestos and</p> <p>8 mesothelioma where the relative risk is 70, you</p> <p>9 know. I mean, we're talking about a much lower</p> <p>10 thing.</p> <p>11 Q. And, again, we've talked already about the</p> <p>12 fact of the IARC noted in its analysis that the</p> <p>13 nonoccupational studies provide a not statistically</p> <p>14 significant association.</p> <p>15 A. Yes.</p> <p>16 MS. O'DELL: Excuse me.</p> <p>17 Q. (BY MR. JAMES) Correct?</p> <p>18 MS. O'DELL: Objection to form.</p> <p>19 You may answer.</p> <p>20 A. I agree with you, but that's why we have</p> <p>21 meta-analyses.</p> <p>22 Q. (BY MR. JAMES) Do you consider a</p> <p>23 limitation to the body of literature looking at</p> <p>24 asbestos and ovarian cancer to include confounding?</p>
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<p>1 didn't cite, I -- I don't believe I -- I don't</p> <p>2 remember it.</p> <p>3 Q. (BY MR. JAMES) Later on in your analysis</p> <p>4 with respect to talc and ovarian cancer you talk</p> <p>5 about the importance of strength, correct?</p> <p>6 A. Part of the Bradford Hill criteria, yes.</p> <p>7 Q. And did you consider strength with respect</p> <p>8 to asbestos and ovarian cancer?</p> <p>9 A. I thought it was interesting that the</p> <p>10 strength of the relative risk or overall risk was</p> <p>11 similar between talc and asbestos.</p> <p>12 For Reid, it was 1.75.</p> <p>13 For Camargo, it was pretty close to</p> <p>14 that. I don't remember the exact number. I don't</p> <p>15 think -- I mean, do you want to know the exact</p> <p>16 number? Wait, wait. I may have said it in my</p> <p>17 report.</p> <p>18 (Examined exhibit.) Yeah, 1.77.</p> <p>19 Yeah, that's almost exactly the same thing and</p> <p>20 almost exactly the same confidence intervals, 1.45,</p> <p>21 2.1, 1.37, 2.28. So they're, you know, so those two</p> <p>22 meta-analyses. Now I forgot -- oh, yes. Strength.</p> <p>23 I thought -- I thought it was</p> <p>24 interesting, yes.</p>	<p>1 A. Tell me what you mean by "confounding."</p> <p>2 Q. What does "confounding" mean to you?</p> <p>3 A. No, no. You asked -- I asked first.</p> <p>4 Q. I know, but I get to ask the questions.</p> <p>5 That's the way it works.</p> <p>6 MS. O'DELL: Object to the form to the</p> <p>7 extent it's vague and there may be some confusion.</p> <p>8 A. For example, I would consider a</p> <p>9 confounding factor that every one of your asbestos</p> <p>10 workers are heavy cigarette smokers.</p> <p>11 Q. (BY MR. JAMES) And I'll ask a more</p> <p>12 precise question now.</p> <p>13 Did you -- do you recall, in reviewing</p> <p>14 the body of literature in asbestos and ovarian</p> <p>15 cancer, that the literature notes an inability to</p> <p>16 account for confounding factors?</p> <p>17 A. Yes. In these studies, they -- they</p> <p>18 don't -- they have not accounted for factors.</p> <p>19 Certainly --</p> <p>20 Q. And --</p> <p>21 A. Yeah.</p> <p>22 Q. I'm sorry.</p> <p>23 MS. O'DELL: Finish your answer if</p> <p>24 you'd like to, Dr. Smith.</p>

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<p style="text-align: right;">Page 138</p> <p>1 A. Like genetic. Smoking, genetics, you</p> <p>2 know, all those things, yes.</p> <p>3 Q. (BY MR. JAMES) And you would agree that</p> <p>4 is a limitation to the set of literature, correct?</p> <p>5 A. Yes.</p> <p>6 Q. Have you heard of a body of literature</p> <p>7 referred to as the Miners and Millers studies.</p> <p>8 Does that ring a bell to you?</p> <p>9 A. It rings a bell.</p> <p>10 Q. Do you know if you reviewed those studies</p> <p>11 in the course of forming your opinions in this case?</p> <p>12 A. I'd have to hear an author, but I remember</p> <p>13 reading about the Miners and Mills [sic] studies.</p> <p>14 Q. Did you know that there's a body of</p> <p>15 literature out there studying cancer rates in miners</p> <p>16 and millers of cosmetic talc?</p> <p>17 MS. O'DELL: Object to the form. It's</p> <p>18 vague, asked and answered.</p> <p>19 A. Without an author, I -- I remember studies</p> <p>20 by author or perhaps by the first initial of the</p> <p>21 author's last name, but I don't remember reading</p> <p>22 something called Miners and Mills studies.</p> <p>23 Q. (BY MR. JAMES) If there is a body of</p> <p>24 literature out there that looks at the cancer rates</p>	<p style="text-align: right;">Page 140</p> <p>1 correct?</p> <p>2 A. I do.</p> <p>3 Q. Do you equate fibrous talc to be -- to be</p> <p>4 also talc-containing asbestiform fibers?</p> <p>5 A. Fibrous talc is an abest- -- asbestiform</p> <p>6 habit of talcum powder. So in that -- in that</p> <p>7 equivalence, they're needlelike particles.</p> <p>8 Q. Do you know if the term "fibrous talc" is</p> <p>9 used in the IARC Monograph?</p> <p>10 A. I believe it is.</p> <p>11 Q. Do you understand if there is a</p> <p>12 distinction between fibrous talc and talc-containing</p> <p>13 asbestiform fibers?</p> <p>14 MS. O'DELL: Objection to form.</p> <p>15 A. I believe -- wait.</p> <p>16 (Examined realtime screen.) I believe</p> <p>17 there is a distinction. I would really like to find</p> <p>18 that part because I know it's in here.</p> <p>19 (Examined exhibit.) Talcum-containing</p> <p>20 asbestiform fibers. Talc may also form true mineral</p> <p>21 fibers that are asbestiform in habit. I used the</p> <p>22 right word.</p> <p>23 "Talc-containing asbestiform fibres is</p> <p>24 a term that's been used inconsistently in the</p>
<p style="text-align: right;">Page 139</p> <p>1 of talc miners and millers and that body of</p> <p>2 literature is not cited in your report, then that</p> <p>3 means you didn't consider that body of literature,</p> <p>4 correct?</p> <p>5 MS. O'DELL: Objection to form;</p> <p>6 misstates the record.</p> <p>7 A. I don't remember reading that paper. I</p> <p>8 hope I did.</p> <p>9 Q. (BY MR. JAMES) Okay. Can you cite to</p> <p>10 me -- I'm sorry, Doctor.</p> <p>11 A. I would hope I did read the paper, but I</p> <p>12 didn't. I don't remember it.</p> <p>13 Q. Can you point to me anywhere in your</p> <p>14 report where you would address studies looking at</p> <p>15 cancer rates in miners and millers of talc?</p> <p>16 A. There is not --</p> <p>17 MS. O'DELL: Objection to the form.</p> <p>18 A. There is not in my report.</p> <p>19 Q. (BY MR. JAMES) Within your report, you</p> <p>20 include some opinions on a phrase that I'll put into</p> <p>21 quotes, "fibrous talc," close quote.</p> <p>22 A. Yes.</p> <p>23 Q. You state in your report that "Asbestos</p> <p>24 and fibrous talc cause epithelial ovarian cancer,"</p>	<p style="text-align: right;">Page 141</p> <p>1 literature. In some contexts, it applies to talc</p> <p>2 containing asbestiform fibres of talc or talc</p> <p>3 intergrown on a nanoscale with other minerals,</p> <p>4 including [sic] anthophyllite."</p> <p>5 So I think they make distinction</p> <p>6 between whether it's asbestos or asbestiform habit</p> <p>7 of talc.</p> <p>8 Am I answering your question?</p> <p>9 Q. (BY MR. JAMES) I think so.</p> <p>10 A. Okay.</p> <p>11 Q. Let me ask you this.</p> <p>12 A. Okay.</p> <p>13 Q. Would you defer to other experts on</p> <p>14 distinctions or characterat- -- characterizations of</p> <p>15 fibrous talc versus talc-containing asbestiform</p> <p>16 fibers?</p> <p>17 MS. O'DELL: Objection; form. She</p> <p>18 just answered your question about that.</p> <p>19 A. I believe many mineralogists know more</p> <p>20 about the forms of talc and minerals than I do.</p> <p>21 I . . .</p> <p>22 Q. (BY MR. JAMES) Have you cited any</p> <p>23 epidemiologic or medical literature that supports</p> <p>24 your opinion that fibrous talc is causative of</p>

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<p>1 ovarian cancer?</p> <p>2 A. I have never seen a study that looks</p> <p>3 specifically with pure fibrous talc and ovarian</p> <p>4 cancer.</p> <p>5 Q. What is the significance of your opinions</p> <p>6 on asbestos to your opinions on talc and ovarian</p> <p>7 cancer?</p> <p>8 MS. O'DELL: Objection to the form.</p> <p>9 A. (Examined realtime screen.) I think the</p> <p>10 presence of asbestos in talcum powder products</p> <p>11 causes ovarian cancer.</p> <p>12 Q. (BY MR. JAMES) Is the alleged presence of</p> <p>13 asbestos in cosmetic talc powders critical to your</p> <p>14 causation opinion that talc powders cause ovarian</p> <p>15 cancer?</p> <p>16 A. No.</p> <p>17 MS. O'DELL: Objection to form.</p> <p>18 Q. (BY MR. JAMES) Do you believe that talc</p> <p>19 powders not contaminated with asbestos would also be</p> <p>20 a cause of ovarian cancer?</p> <p>21 A. I'm not sure there is such a thing as a</p> <p>22 pure, platy talc powder, but I believe such powder</p> <p>23 use, did it exist, would cause ovarian cancer.</p> <p>24 Q. Would your answer hold true if I asked the</p>	<p>1 A. Okay. You gave me a --</p> <p>2 MS. O'DELL: Let him -- excuse me.</p> <p>3 Let him ask the question and then you respond.</p> <p>4 THE WITNESS: Okay.</p> <p>5 Q. (BY MR. JAMES) (Examined realtime</p> <p>6 screen.) So the question that I asked was: Do you</p> <p>7 believe that talc that does not contain fibrous talc</p> <p>8 is a cause of ovarian cancer?</p> <p>9 MS. O'DELL: Object to the form.</p> <p>10 A. Yes.</p> <p>11 Q. (BY MR. JAMES) If talc powders did not</p> <p>12 contain asbestos or fibrous talc, would your</p> <p>13 opinions about mechanism change?</p> <p>14 A. This is kind of a double negative, doesn't</p> <p>15 it?</p> <p>16 MS. O'DELL: Object to the form.</p> <p>17 Q. (BY MR. JAMES) I don't think it's a</p> <p>18 double negative.</p> <p>19 A. Okay.</p> <p>20 (Examined realtime screen.) My</p> <p>21 opinion about mechanisms unchanged by concerns of</p> <p>22 asbestos in fibrous talc.</p> <p>23 MR. JAMES: It's 12:32. I can</p> <p>24 continue a little longer if you'd like or -- it's up</p>
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<p>1 same question about fibrous talc?</p> <p>2 MS. O'DELL: Just to be clear --</p> <p>3 MR. JAMES: And if you'd like -- I'll</p> <p>4 just go through it again, which is no problem.</p> <p>5 Q. (BY MR. JAMES) Is the alleged presence of</p> <p>6 fibrous talc critical to your causation opinion that</p> <p>7 talcum powders cause ovarian cancer?</p> <p>8 MS. O'DELL: Object to the word</p> <p>9 "alleged."</p> <p>10 You may answer.</p> <p>11 A. I believe that fibr- -- fibrous talc -- a</p> <p>12 poor preparation of fibrous talc applied repeatedly</p> <p>13 and consistently to the perineum would cause ovarian</p> <p>14 cancer.</p> <p>15 Q. (BY MR. JAMES) And let me ask a question,</p> <p>16 maybe, that's more precise, similar to the question</p> <p>17 I asked you about asbestos.</p> <p>18 Do you believe that talc that does not</p> <p>19 contain fibrous talc is a cause of ovarian cancer?</p> <p>20 A. I already answered that.</p> <p>21 MS. O'DELL: Object to the form.</p> <p>22 A. But I -- but --</p> <p>23 Q. (BY MR. JAMES) I think maybe we missed</p> <p>24 each other.</p>	<p>1 to you Leigh and Dr. Smith.</p> <p>2 MS. O'DELL: Dr. Smith, would you like</p> <p>3 to take a break for lunch now or --</p> <p>4 THE WITNESS: Have you got a 10-minute</p> <p>5 block?</p> <p>6 MR. JAMES: I can always go for 10</p> <p>7 more minutes.</p> <p>8 THE WITNESS: Let's do it.</p> <p>9 MR. JAMES: Okay.</p> <p>10 THE WITNESS: Is that -- is everybody</p> <p>11 else comfortable? Yeah, I don't want to --</p> <p>12 MS. O'DELL: Yeah. 10 minutes and</p> <p>13 let's --</p> <p>14 THE WITNESS: -- make somebody --</p> <p>15 BY MS. O'DELL: -- take a break.</p> <p>16 THE WITNESS: -- endure hunger pains.</p> <p>17 Q. (BY MR. JAMES) All right. Dr. Smith,</p> <p>18 we're gonna wade back into your report --</p> <p>19 A. Oh, good.</p> <p>20 Q. -- and I'm looking at page 3.</p> <p>21 And on page 3, Dr. Smith, you list</p> <p>22 what you consider to be, quote, "generally</p> <p>23 accepted," close quote, risk factors for ovarian</p> <p>24 cancer, correct?</p>

37 (Pages 142 to 145)

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<p>1 A. I see that.</p> <p>2 Q. What is your definition of a generally</p> <p>3 accepted risk factor?</p> <p>4 A. Something that the vast majority of</p> <p>5 trained physicians in that specialty would accept as</p> <p>6 truth.</p> <p>7 Q. And how did you compile this list?</p> <p>8 A. Working in the field for 40 years, viewing</p> <p>9 lots of risk articles and tabulating them, like</p> <p>10 listing them and reviewing the literature regarding</p> <p>11 specific things.</p> <p>12 For example, a comprehensive view of</p> <p>13 the literature regarding tubal sterilization and its</p> <p>14 risk of ovarian cancer.</p> <p>15 Throughout my career, numerous times,</p> <p>16 I've done ovarian contraceptive use and ovarian</p> <p>17 cancer of use as formulations of oral contraceptives</p> <p>18 have changed and different progestins, different</p> <p>19 levels of estrogen, do we still have a suppressive</p> <p>20 effect on ovarian cancer? So this is kind of my</p> <p>21 life.</p> <p>22 Q. Do you believe all of the factors that</p> <p>23 you've listed here in this first paragraph are</p> <p>24 mentioned in the articles here that you've cited?</p>	<p>1 A. What's -- oh, intrauterine devices. I</p> <p>2 don't think that's generally -- it's been -- it's</p> <p>3 been studied in some studies. Pelvic inflammatory</p> <p>4 disease, it's been plus or minus in some studies.</p> <p>5 Q. So --</p> <p>6 A. But --</p> <p>7 Q. I'm sorry.</p> <p>8 A. -- somebody mentioned it somewhere in</p> <p>9 my -- in my life.</p> <p>10 Q. And so the way you've characterized this</p> <p>11 paragraph is that you have attempted to list, quote,</p> <p>12 "generally accepted," close quote, risk factors.</p> <p>13 And what I'm asking you is whether all</p> <p>14 these things that you've listed here are, in your</p> <p>15 opinion, generally accepted by the medical</p> <p>16 community?</p> <p>17 A. I will give you that intrauterine devices</p> <p>18 may not be generally accepted by the majority of --</p> <p>19 I lost my mike. I'm sorry -- obstetrician</p> <p>20 gynecologists.</p> <p>21 Q. And how about PID? Do you believe that's</p> <p>22 a generally accepted risk factor with the</p> <p>23 terminology you've used?</p> <p>24 A. There -- there are a whole bunch of papers</p>
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<p>1 A. I'm not -- without going to each</p> <p>2 individual article, I can't checklist which thing is</p> <p>3 listed in each article.</p> <p>4 Q. Was it -- when you created this list, was</p> <p>5 it your intention to cite to an authority that</p> <p>6 supported each one of these things that you listed</p> <p>7 at least once?</p> <p>8 A. I think -- I don't think everyone -- I</p> <p>9 can't promise you, without looking at each of these</p> <p>10 papers, that everybody listed every single one of</p> <p>11 the things I said, but somebody in this group</p> <p>12 mentioned these things, and I had other information</p> <p>13 that maybe want to put on the list.</p> <p>14 Q. Is it possible that at least some of these</p> <p>15 things that you've listed are not identified in the</p> <p>16 sources that you've cited and instead come from the</p> <p>17 information that you just referred to that -- that</p> <p>18 you possessed through your practice?</p> <p>19 A. It's possible.</p> <p>20 MS. O'DELL: Object to form.</p> <p>21 A. It's possible.</p> <p>22 Q. (BY MR. JAMES) For -- for example, IUDs</p> <p>23 that you listed here, do you believe that's a</p> <p>24 general accepted risk factor for ovarian cancer?</p>	<p>1 about pelvic inflammatory disease and its impact on</p> <p>2 ovarian cancer and epidemiologic studies and they</p> <p>3 vary in value.</p> <p>4 I would -- it is not as strong a risk</p> <p>5 factor as inherited gene mutations, family history,</p> <p>6 nulliparity, and endometriosis.</p> <p>7 Q. When creating this list of generally</p> <p>8 accepted risk factors, did you consult a list of</p> <p>9 risk factors published by any medical or scientific</p> <p>10 organization?</p> <p>11 MS. O'DELL: Object to the form.</p> <p>12 But you . . .</p> <p>13 A. I didn't go on any websites to get my</p> <p>14 references.</p> <p>15 Q. (BY MR. JAMES) Would you have consulted</p> <p>16 the list of risk factors published by ACOG?</p> <p>17 A. I didn't get the -- even the committee</p> <p>18 opinion or the postgraduate, all those different</p> <p>19 letters, I didn't use that as one of my resources.</p> <p>20 Q. And did you consider a list of risk</p> <p>21 factors published by the SGL?</p> <p>22 A. I did not use that as one of my risk</p> <p>23 factors.</p> <p>24 Q. Do you recognize both of those</p>

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<p>1 organizations as respected scientific organizations?</p> <p>2 A. I do.</p> <p>3 Q. And you're members of both, correct?</p> <p>4 A. I am.</p> <p>5 Q. And you have been active in both, correct?</p> <p>6 A. Very.</p> <p>7 Q. In crafting a list of generally accepted</p> <p>8 risk factors, why wouldn't you have been interested</p> <p>9 in what those two organizations have to say about</p> <p>10 what is, quote, "generally accepted"?</p> <p>11 A. I'm not disinterested. I, again,</p> <p>12 assembled my own sources out of medical databases</p> <p>13 and read the articles and did my own work.</p> <p>14 It's not that I disagree with them.</p> <p>15 It's just I don't want a copy of their stuff, you</p> <p>16 know. I want to do my own work.</p> <p>17 Q. Earlier you defined "generally</p> <p>18 accepted" -- and I'll see if I can find it on my</p> <p>19 realtime.</p> <p>20 While I'm looking for it, and you can</p> <p>21 correct me if I've misstated it, Dr. Smith, but my</p> <p>22 recall is that you defined "generally accepted" as</p> <p>23 something that is believed by the majority of</p> <p>24 practitioners in the field.</p>	<p>1 I can't give you a percentage, like</p> <p>2 have a vote in ACOG of who calls it a risk factor</p> <p>3 and who doesn't. So I don't know what proportion of</p> <p>4 OB/GYNs believe that's a risk factor or not, but</p> <p>5 certainly some do, and I can't quantitate it</p> <p>6 further.</p> <p>7 Q. (BY MR. JAMES) And to say something is</p> <p>8 generally accepted, you'd have to quantify it,</p> <p>9 wouldn't you?</p> <p>10 MS. O'DELL: Object to the form.</p> <p>11 A. Yeah. I think generally it would be at</p> <p>12 51 percent, and I don't know where the count is.</p> <p>13 Q. (BY MR. JAMES) And do you know that the</p> <p>14 ACOG has actually issued a statement on the</p> <p>15 talc/ovarian cancer hypothesis?</p> <p>16 MS. O'DELL: Object to the form.</p> <p>17 A. I have read a very brief statement on the</p> <p>18 ACOG website about talc.</p> <p>19 Q. (BY MR. JAMES) And, again, is -- so</p> <p>20 because you consider it to be a well-respected</p> <p>21 organization, you would be interested in what that</p> <p>22 organization has to say about the hypothesis,</p> <p>23 correct?</p> <p>24 A. That's why I looked it up.</p>
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<p>1 Is that a fair summary?</p> <p>2 A. Yes.</p> <p>3 Q. Wouldn't it be logical that statements by</p> <p>4 medic- -- respected medical and scientific</p> <p>5 organizations with regard to risk factors would be</p> <p>6 reflective of what the medical community believes --</p> <p>7 A. Yes.</p> <p>8 Q. -- as a whole?</p> <p>9 MS. O'DELL: Object to the form.</p> <p>10 Q. (BY MR. JAMES) Among that list in the</p> <p>11 same paragraph, you have listed all of the risk</p> <p>12 factors.</p> <p>13 You also list talc and asbestos,</p> <p>14 correct?</p> <p>15 A. Yes.</p> <p>16 Q. And the way you phrase it, I want to be</p> <p>17 sure that I understand your testimony, but are you</p> <p>18 testifying here that talcum powder and asbestos are</p> <p>19 generally accepted risk factors for ovarian cancer?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A. They are not on the SGO list. They are</p> <p>22 not -- I mean, on the ACOG list. They are listed in</p> <p>23 some review articles and the literature about them</p> <p>24 in risk factors. They are not listed in others.</p>	<p>1 Q. And do you -- did you -- do you recall, if</p> <p>2 you've looked at that statement, that they say that</p> <p>3 there is, quote, "No medical consensus that talcum</p> <p>4 powder causes ovarian cancer," closed quote?</p> <p>5 A. That was the final line, I think, a first</p> <p>6 line -- first part of what I read was "Don't use it"</p> <p>7 because of the -- I can't -- I can't quote it out of</p> <p>8 my brain. But just the "Don't use talc." We</p> <p>9 haven't got medical consistent is the very short</p> <p>10 statement I remember reading some time ago.</p> <p>11 Q. Okay. I'm gonna mark that, the ACOG</p> <p>12 statement that I'm discussing --</p> <p>13 A. Oh. Well, good.</p> <p>14 Q. -- with you, Dr. Smith, as Exhibit</p> <p>15 Number 11.</p> <p>16 A. Don't make me dig so far back.</p> <p>17 MS. O'DELL: Exhibit 11?</p> <p>18 MR. JAMES: Yes.</p> <p>19 BY MS. O'DELL: Thank you.</p> <p>20 MR. JAMES: That's where we are.</p> <p>21 BY MS. O'DELL: Is this the . . .</p> <p>22 MR. JAMES: And I'm sorry for the</p> <p>23 small print.</p> <p>24 (Line intentionally left blank.)</p>

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<p style="text-align: right;">Page 154</p> <p>1 (Deposition Exhibit 11 marked for 2 identification.) 3 A. (Examined exhibit.) Okay. "Obstetrician 4 gynecologists do not remend -- recommend use of 5 vaginal treatment such as douche, vaginal sprays or 6 talcum powder and the use of talcum powder has 7 declined over the years. There is no medical 8 consensus that talcum powder causes ovarian cancer." 9 Q. (BY MR. JAMES) Right. And so we've 10 talked about that last sentence already, correct, 11 where they -- ACOG has published a statement saying 12 there's not a medical consensus, correct? 13 A. Yes. 14 Q. Okay. And the first portion of the 15 statement that you've read into the record about the 16 gynecologists not recommending the use -- 17 A. Um-hum. 18 Q. -- can you read the first part of that 19 sentence for me? 20 A. "Because of concerns regarding potential 21 discomfort or pain." 22 Q. And so the recommendation to not use the 23 talcum powder products there is predicated on 24 concern for discomfort or pain, correct?</p>	<p style="text-align: right;">Page 156</p> <p>1 don't want women to use talcum powder products and 2 aren't willing to call its relation to ovarian 3 cancer. 4 Q. (BY MR. JAMES) Do you know Dr. Hal 5 Lawrence? 6 A. I do. Blue-eyed boy. 7 Q. Have you reached out to him with any 8 concerns about the statement and how -- 9 A. No, I have not. 10 Q. -- it's phrased? 11 MS. O'DELL: Dr. Smith, let him 12 finish, please, with his question -- 13 THE WITNESS: Oh, I'm sorry. 14 MS. O'DELL: -- just so it's clear on 15 the record. 16 MR. JAMES: Okay. I'm about to the 17 breaking point, I believe. I'm gonna mark as the 18 next two exhibits, Exhibit 12. 19 THE WITNESS: I'm out of order. 20 MS. O'DELL: That's okay. We'll do it 21 a -- 22 THE WITNESS: I don't want to lose 23 any. I don't. 24 MS. O'DELL: They're all there.</p>
<p style="text-align: right;">Page 155</p> <p>1 MS. O'DELL: Object to the form. 2 A. That's what it says, but -- so -- and the 3 number of references they cite here are puny 4 compared to a number of studies that I reviewed 5 in-depth. I -- 6 Q. (BY MR. JAMES) Do you believe the ACOG -- 7 MS. O'DELL: Excuse me, sir. Let her 8 finish the -- 9 Q. (BY MR. JAMES) Oh, I'm sorry. I thought 10 you were. 11 MS. O'DELL: Yeah. 12 You may finish, Dr. Smith, if you'd 13 like. 14 A. Reading between the lines and knowing some 15 of the people involved, they don't want to incur 16 criticism for saying, "Because of our concerns about 17 a potential for the development of ovarian cancer, 18 obstetrician gynecologists do not recommend the use 19 of vaginal treatments," so they threw in "potential 20 discomfort or pain." 21 Now, women frequently use douches, 22 sprays, or powder because they're uncomfortable. 23 It's not because they cause discomfort. 24 So the people behind the statement</p>	<p style="text-align: right;">Page 157</p> <p>1 THE WITNESS: Here. I got some over 2 here. Sorry. 3 (Deposition Exhibit 12 marked for 4 identification.) 5 Q. (BY MR. JAMES) All right. Dr. Smith, 6 what I've handed you is the publication of risk 7 factors for ovarian cancer published by the SGA -- 8 SGO. 9 A. Yes. 10 Q. Just for the record, Dr. Smith, is this 11 the list that you consulted in forming your opinions 12 in this case? 13 MS. O'DELL: Object to the form; 14 misstates her testimony. I think she said she 15 didn't consult the list. 16 A. Yeah, I didn't read this for writing my 17 report. 18 Q. (BY MR. JAMES) Okay. I thought earlier 19 you testified -- 20 A. I've looked them up. 21 Q. -- that you -- I'm sorry. Well, we're so 22 close. 23 A. I interrupted you. I'm sorry. 24 Q. No. We're both doing it now, but we're</p>

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<p>1 close.</p> <p>2 I'm sorry. I thought you acknowledged</p> <p>3 earlier that you were aware that talc was not listed</p> <p>4 as a risk factor on -- on the SGO's list.</p> <p>5 MS. O'DELL: That's a different</p> <p>6 question, Counsel, but --</p> <p>7 A. Yes, sir, I was aware of that.</p> <p>8 Q. (BY MR. JAMES) Okay. So at some point</p> <p>9 you've read the list, correct?</p> <p>10 A. Yes.</p> <p>11 Q. Did you -- have -- when is the last time</p> <p>12 you've read the list?</p> <p>13 A. I -- the last time I read the list was</p> <p>14 probably in the past two weeks. I did not use this</p> <p>15 list in the preparation of my report. I didn't use</p> <p>16 this as a source.</p> <p>17 Q. And you didn't cite to it?</p> <p>18 A. And I didn't cite it.</p> <p>19 Q. And you didn't discuss it at all?</p> <p>20 A. And I didn't discuss it at all.</p> <p>21 Q. You agree it's relevant when opining on</p> <p>22 what risk factors are generally accepted, correct?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A. (Examined exhibit.) I'm sorry. I was</p>	<p>1 Q. And before we break, Doctor, just for</p> <p>2 purposes of the record, I also want to confirm: At</p> <p>3 some point, you have looked at a list of risk</p> <p>4 factors for ovarian cancer published by ACOG,</p> <p>5 correct?</p> <p>6 A. Yes.</p> <p>7 Q. And earlier you acknowledged that talc was</p> <p>8 not listed on that --</p> <p>9 A. Yes.</p> <p>10 Q. -- list, correct?</p> <p>11 A. Yes.</p> <p>12 Q. And so I'm -- it's -- and, again, it's</p> <p>13 something that you have not cited or discussed in</p> <p>14 your report, correct?</p> <p>15 A. (Nodded head.)</p> <p>16 Q. So I'm going to hand you what I'm marking</p> <p>17 as Exhibit Number 13 to confirm that this is, in</p> <p>18 fact, what you've looked at. Okay?</p> <p>19 (Deposition Exhibit 13 marked for</p> <p>20 identification.)</p> <p>21 A. (Examined exhibit.) Okay.</p> <p>22 Q. (BY MR. JAMES) Does that list -- does</p> <p>23 that publication that I've handed you look familiar</p> <p>24 to you?</p>
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<p>1 reading it.</p> <p>2 MS. O'DELL: Take a moment if you need</p> <p>3 to, Doctor, to read it.</p> <p>4 A. (Examined exhibit.) I see something here</p> <p>5 that I can say is not permanent -- is not -- I</p> <p>6 disagree with. Let's put it that way. I disagree</p> <p>7 with.</p> <p>8 Yes, women who -- yes. I mean, age</p> <p>9 is -- you know, when -- when you read all these</p> <p>10 papers on risk factors, aging is a risk factor for</p> <p>11 the development of ovarian cancer, and this is one</p> <p>12 of the few places that I say -- that I see actually</p> <p>13 say, "Yeah, the older you get, the higher your</p> <p>14 risk," because that's just the way it is.</p> <p>15 They say women who have had</p> <p>16 gynecologic surgery makes them at increased risk for</p> <p>17 ovarian cancer, and I have never seen that before.</p> <p>18 I -- I can't remember seeing that anywhere.</p> <p>19 And I've certainly seen hysterectomy</p> <p>20 decreases value and tubal ligation decreases value,</p> <p>21 but having that in the increase, that is not</p> <p>22 something I've ever seen. I'd like to see the</p> <p>23 studies that show that.</p> <p>24 Okay. So my comments are done.</p>	<p>1 A. Yes.</p> <p>2 Q. Is that what you reviewed before,</p> <p>3 Dr. Smith --</p> <p>4 A. I've seen it before.</p> <p>5 Q. -- with respect to ACOG?</p> <p>6 A. I've seen it before.</p> <p>7 Q. Do you consider it relevant to the</p> <p>8 opinions that you're offering in this case?</p> <p>9 A. It is relevant to the conversation.</p> <p>10 Q. Is it relevant to an opinion about whether</p> <p>11 something is generally accepted or not?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A. It's accepted by the members of -- or at</p> <p>14 least the steering committee of ACOG, and I -- this</p> <p>15 is pretty bland. It's -- I think most people would</p> <p>16 agree with these risk -- risk factors.</p> <p>17 MR. JAMES: Is now time for a break</p> <p>18 everyone?</p> <p>19 THE WITNESS: I'm up for it.</p> <p>20 THE VIDEOGRAPHER: Going off the</p> <p>21 record. The time is 12:54 p.m.</p> <p>22</p> <p>23 (A lunch recess taken from 12:54 p.m.</p> <p>24 to 2:03 p.m.)</p>

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<p style="text-align: right;">Page 162</p> <p>1 AFTERNOON SESSION</p> <p>2 THE VIDEOGRAPHER: Back on the record.</p> <p>3 The time is 2:03 p.m.</p> <p>4 EXAMINATION (CONTINUED)</p> <p>5 BY MR. JAMES:</p> <p>6 Q. Dr. Smith, are we ready to proceed?</p> <p>7 A. We are.</p> <p>8 Q. Great.</p> <p>9 In compiling your list of generally</p> <p>10 accepted risk factors, did you consult the NCI's</p> <p>11 list of risk factors for ovarian cancer?</p> <p>12 A. I did not.</p> <p>13 Q. Okay. Are you aware that the NCI has</p> <p>14 listed risk factors in the publication referred to</p> <p>15 as the PDQ?</p> <p>16 A. I know they have PDQs. I have not read</p> <p>17 that PDQ.</p> <p>18 Q. You recognize the NCI, the National Cancer</p> <p>19 Institute, as a respected scientific organization?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A. Yes.</p> <p>22 Q. (BY MR. JAMES) And I've seen references</p> <p>23 to the NC- -- NCI in your report, correct?</p> <p>24 A. Yes.</p>	<p style="text-align: right;">Page 164</p> <p>1 this page. I have seen it before.</p> <p>2 Q. So you've seen this PDQ document?</p> <p>3 A. Yes, I have.</p> <p>4 Q. And this document is not cited or</p> <p>5 discussed in your report, correct?</p> <p>6 A. It is not.</p> <p>7 Q. Why is that?</p> <p>8 A. I prefer to use peer-reviewed references</p> <p>9 rather than organizational websites or PDQs.</p> <p>10 Q. And you reference other organizations in</p> <p>11 your report, correct?</p> <p>12 A. Give me an example.</p> <p>13 Q. For example, do you reference IARC in your</p> <p>14 report?</p> <p>15 A. Oh, yes.</p> <p>16 Q. Okay. But here you decided not to</p> <p>17 recognize the NCI PDQ, correct?</p> <p>18 MS. O'DELL: Object to the form.</p> <p>19 A. I think they're a different level of -- of</p> <p>20 standard between IARC and the PDQ.</p> <p>21 Q. (BY MR. JAMES) Are you familiar with the</p> <p>22 process employed to prepare the PDQ that's in front</p> <p>23 of you right now?</p> <p>24 A. I do not know what method that is.</p>
<p style="text-align: right;">Page 163</p> <p>1 Q. And they're a frequent sponsor of studies</p> <p>2 and --</p> <p>3 A. Yes.</p> <p>4 Q. -- cancer research, correct?</p> <p>5 A. Yes.</p> <p>6 Q. I'm gonna mark as Exhibit Number 14 the</p> <p>7 NCI PDQ on Ovarian Cancer Prevention, Health</p> <p>8 Professional Version.</p> <p>9 (Deposition Exhibit 14 marked for</p> <p>10 identification.)</p> <p>11 Q. (BY MR. JAMES) And, Dr. Smith, is this</p> <p>12 the first time that you've seen this document?</p> <p>13 A. I believe so.</p> <p>14 Q. Okay. If you turn to -- unfortunately,</p> <p>15 it's not paginated. I'll do a manual count for you.</p> <p>16 If you flip seven pages and look on</p> <p>17 the backside of this double-sided copy.</p> <p>18 A. (Complied.) Okay.</p> <p>19 Q. Okay. At the top of that page there's a</p> <p>20 section titled, "Factors With Inadequate Evidence of</p> <p>21 an Association Risk of -- of Ovarian, Fallopian</p> <p>22 Tube, and Primary Peritoneal Cancer."</p> <p>23 Do you see where I'm reading?</p> <p>24 A. Yes. And do you know what, I recognize</p>	<p style="text-align: right;">Page 165</p> <p>1 Q. We see here on this PDQ on the page that I</p> <p>2 referred you to --</p> <p>3 A. Um-hum.</p> <p>4 Q. -- that below the category of "Factors</p> <p>5 With Inadequate Evidence," you see there that</p> <p>6 "Perineal talc exposure" is listed, correct?</p> <p>7 A. Yes.</p> <p>8 Q. Okay. And can you read that first</p> <p>9 sentence for me in the section right there?</p> <p>10 A. "The weight of evidence does not support</p> <p>11 an association between perineal talc exposure and an</p> <p>12 increased risk of ovarian cancer."</p> <p>13 Q. And your litigation opinion offered here</p> <p>14 today is different than what the NCI states here,</p> <p>15 correct?</p> <p>16 A. Yes, it is.</p> <p>17 Q. In determining whether something is</p> <p>18 generally accepted, do you believe it would be</p> <p>19 appropriate to consult what the National Cancer</p> <p>20 Institute says with respect to the association</p> <p>21 between ovarian cancer and talc?</p> <p>22 MS. O'DELL: Object to the form.</p> <p>23 A. I have told you that I have seen this and</p> <p>24 I looked at the references they cited, which is a</p>

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<p>1 very limited portion of the medical literature.</p> <p>2 This is not an exhausted list of</p> <p>3 references. Certainly it lacks the most recent</p> <p>4 meta-analyses, so I think they didn't look at enough</p> <p>5 stuff.</p> <p>6 Q. (BY MR. JAMES) Do you think the recent</p> <p>7 meta-analyses are the -- are pieces of literature</p> <p>8 that are critical to the causation opinion --</p> <p>9 opinion you're reaching here today?</p> <p>10 MS. O'DELL: Object to the form.</p> <p>11 A. I believe they are more comprehensive and</p> <p>12 highly supportive.</p> <p>13 Q. (BY MR. JAMES) And the question that I</p> <p>14 asked earlier, I think that maybe I didn't get an</p> <p>15 answer to.</p> <p>16 Do you believe when opining about</p> <p>17 whether something is generally accepted it would be</p> <p>18 appropriate to consult what the National Cancer</p> <p>19 Institute has to say about the topic?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A. I've read it. It's not worthy of</p> <p>22 citation.</p> <p>23 Q. (BY MR. JAMES) Do you believe the opinion</p> <p>24 published by the NCI with respect to risk factors</p>	<p>1 ovarian cancer, you have also opined that talc is a</p> <p>2 generally accepted risk factor for ovarian cancer.</p> <p>3 Do you understand the distinction</p> <p>4 between those two opinions?</p> <p>5 MS. O'DELL: Object to form.</p> <p>6 A. I understand the difference in -- of those</p> <p>7 opinions.</p> <p>8 Q. (BY MR. JAMES) And with respect to the</p> <p>9 latter opinion, the opinion about what is generally</p> <p>10 accepted by the medical community, would you agree</p> <p>11 that the statement provided by the NCI in its PDQ is</p> <p>12 relevant to determining what is generally accepted</p> <p>13 as a risk factor?</p> <p>14 MS. O'DELL: Object to the form.</p> <p>15 A. I don't -- I don't think that physicians</p> <p>16 go to the PDQ and say, "If that's what the NCI says,</p> <p>17 that's what I believe."</p> <p>18 To find out the number of, for</p> <p>19 example, obstetricians/gynecologists who believe</p> <p>20 talcum powder products are a significant contributor</p> <p>21 to ovarian cancer, I believe to answer that</p> <p>22 question, we'd have to survey those people.</p> <p>23 Q. (BY MR. JAMES) I think I've asked my</p> <p>24 question enough times there.</p>
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<p>1 and ovarian cancer is informative to your opinion</p> <p>2 about what is generally accepted as a risk factor</p> <p>3 for ovarian cancer?</p> <p>4 MS. O'DELL: Object to the form.</p> <p>5 A. I sought other references in peer-reviewed</p> <p>6 journals to compile my risk factor list.</p> <p>7 Q. (BY MR. JAMES) Do you believe the NCI PDQ</p> <p>8 paper is relevant to forming an opinion about what</p> <p>9 is generally accepted by the medical community?</p> <p>10 MS. O'DELL: Objection --</p> <p>11 A. It is not relevant --</p> <p>12 MS. O'DELL: Excuse me. Objection;</p> <p>13 asked and answered.</p> <p>14 A. It is not relevant to my opinion because</p> <p>15 it is not comprehensive.</p> <p>16 Q. (BY MR. JAMES) And when you say it's not</p> <p>17 relevant to your opinion, are you speaking about</p> <p>18 your opinion on causation?</p> <p>19 A. Yes.</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 Q. (BY MR. JAMES) And --</p> <p>22 A. Well, and risk factor. Yes, all of it.</p> <p>23 Q. But in your report you've -- in addition</p> <p>24 to opine -- opining that talc is causative of</p>	<p>1 What risk factors for ovarian cancer</p> <p>2 do you believe have been scientifically demonstrated</p> <p>3 to be synergistic or additive?</p> <p>4 MS. O'DELL: Object to the form.</p> <p>5 You may answer.</p> <p>6 A. BRCA and -- BRCA 1 and 2 status in oral</p> <p>7 contraceptive use has been demonstrated to be</p> <p>8 additive.</p> <p>9 Tubal ligation with nulliparity and</p> <p>10 other higher risk factors.</p> <p>11 The -- I'm looking up the name of the</p> <p>12 author again.</p> <p>13 MS. O'DELL: What are you referring</p> <p>14 to, Dr. Smith?</p> <p>15 (Deposition Exhibit 15 referenced.)</p> <p>16 A. The multiple risk factor studies of</p> <p>17 Vitonis, Titus-Ernstoff, and Cramer, 2011 and their</p> <p>18 five risk factors, one of which was talc, were</p> <p>19 cumulative in increasing your risk for -- as a</p> <p>20 scoring system for increasing your risk of ovarian</p> <p>21 cancer, so that's clearly an additive study. It</p> <p>22 doesn't look at synergy.</p> <p>23 Q. (BY MR. JAMES) So the Vitonis study that</p> <p>24 you mentioned you're saying looks at cumulativeness,</p>

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<p>1 but not synergy, correct?</p> <p>2 A. Synergy to me means you put two things</p> <p>3 together and they're bigger than their sum. And I</p> <p>4 haven't seen that in ovarian cancer risk factors.</p> <p>5 Q. As a whole or with respect to talc?</p> <p>6 MS. O'DELL: Object to form.</p> <p>7 A. As a whole.</p> <p>8 Q. (BY MR. JAMES) So you don't have an</p> <p>9 opinion that -- let me start over.</p> <p>10 Are there any ovarian cancer risk</p> <p>11 factors that you believe have been scientifically</p> <p>12 demonstrated to be synergistic?</p> <p>13 A. I can't think of any at this time.</p> <p>14 Q. Are there any risk factors for ovarian</p> <p>15 cancer that you believe have been scientifically</p> <p>16 demonstrated to be additive?</p> <p>17 A. Yes.</p> <p>18 Q. And what are those?</p> <p>19 MS. O'DELL: Objection; asked and</p> <p>20 answered.</p> <p>21 A. I just answered that question.</p> <p>22 THE WITNESS: May I see the Vitonis</p> <p>23 paper, please?</p> <p>24 MS. O'DELL: Sure.</p>	<p>1 additive.</p> <p>2 Q. And so this paper is discussing a</p> <p>3 hypothesis, correct?</p> <p>4 MS. O'DELL: Object to the form.</p> <p>5 A. That this paper has attempted to develop a</p> <p>6 risk factor score that may estimate patients who do</p> <p>7 not have documented genetic predisposition to</p> <p>8 ovarian cancer, so eliminating that possibility.</p> <p>9 And now -- or they're trying to</p> <p>10 develop a risk factor based score system to advise</p> <p>11 physicians on when to include oophorectomy with</p> <p>12 hysterectomy and salpingectomy.</p> <p>13 Q. (BY MR. JAMES) If you look with me at the</p> <p>14 first page in the Conclusion section of the</p> <p>15 abstract, Dr. Smith --</p> <p>16 A. Um-hum.</p> <p>17 Q. -- do you see there where it says that "We</p> <p>18 developed a risk-assessment tool that can quantify</p> <p>19 women's risk for ovarian cancer and should be</p> <p>20 validated in other data sets."</p> <p>21 Do you see that language?</p> <p>22 A. Yes.</p> <p>23 Q. Okay. Do you acknowledge that this paper</p> <p>24 represents a hypothesis?</p>
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<p>1 MR. JAMES: I'm gonna mark the Vitonis</p> <p>2 paper as Exhibit 15.</p> <p>3 (Deposition Exhibit 15 marked for</p> <p>4 identification.)</p> <p>5 (Discussion off the record.)</p> <p>6 Q. (BY MR. JAMES) Before we dig into the</p> <p>7 paper, Dr. Smith, and this may help move us along,</p> <p>8 in your report, you used the terminology</p> <p>9 "cumulative," "additive," and "synergistic."</p> <p>10 A. I do.</p> <p>11 Q. So synergistic we have discussed already,</p> <p>12 correct?</p> <p>13 A. Correct.</p> <p>14 Q. Do you believe "cumulative" and "additive"</p> <p>15 mean the same thing?</p> <p>16 A. Not necessarily.</p> <p>17 Q. Do you believe that it has been</p> <p>18 scientifically demonstrated that talc is cumulative</p> <p>19 with other risk factors?</p> <p>20 A. I'm not aware of such a paper.</p> <p>21 Q. Do you believe it has been scientifically</p> <p>22 demonstrated that talc is additive with other risk</p> <p>23 factors?</p> <p>24 A. I believe this paper suggests it's</p>	<p>1 MS. O'DELL: Object to the form.</p> <p>2 A. I -- it has not been validated by other</p> <p>3 studies that I am aware of.</p> <p>4 Q. (BY MR. JAMES) Okay. Dr. Smith, on</p> <p>5 page 9 you begin your review of the epidemiologic</p> <p>6 literature, correct?</p> <p>7 A. Yes, sir.</p> <p>8 Q. Okay. And I'm referring you there because</p> <p>9 we'll spend a little bit of the time walking through</p> <p>10 it together. Okay?</p> <p>11 A. Okay.</p> <p>12 Q. You start your analysis with a discussion</p> <p>13 of meta-analyses in the pooled study, correct?</p> <p>14 A. Correct.</p> <p>15 Q. What limitations do you believe there are</p> <p>16 with meta-analyses in general?</p> <p>17 A. Meta-analyses are statistical studies of</p> <p>18 single -- single site epidemiologic studies, but</p> <p>19 they are still retrospective in the tiers of level</p> <p>20 of evidence in medicine, case control, and cohort</p> <p>21 studies.</p> <p>22 All epidemiologic studies are all</p> <p>23 listed at Level 4, which is obviously not the</p> <p>24 highest level of evidence. So that's a big</p>

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<p style="text-align: right;">Page 174</p> <p>1 limitation to start with.</p> <p>2 Q. Any other limitations that you can</p> <p>3 identify, sitting here today, with respect to</p> <p>4 meta-analyses?</p> <p>5 A. I am not an expert on statistical methods,</p> <p>6 but I know there are multiple different statistical</p> <p>7 tools to perform meta-analyses, and I'm sure a</p> <p>8 biostatistician could give you a better discussion</p> <p>9 of that.</p> <p>10 Q. So on page 9, you start with your</p> <p>11 discussion of the 1992 Harlow meta-analysis,</p> <p>12 correct?</p> <p>13 A. Correct.</p> <p>14 Q. How would you characterize the odds ratio</p> <p>15 reported in that meta-analysis?</p> <p>16 MS. O'DELL: Object to the form.</p> <p>17 A. It's -- the authors conclude there's</p> <p>18 associated, albeit modest, between ovarian cancer</p> <p>19 and peritoneal talc use.</p> <p>20 In their study, their meta-analysis</p> <p>21 was 1.5, 0.9; but in all studies involved for 1100</p> <p>22 patients, which is still a really small number,</p> <p>23 it's 1.3, confidence intervals 1.1 to 1.6.</p> <p>24 Q. (BY MR. JAMES) And just to be clear,</p>	<p style="text-align: right;">Page 176</p> <p>1 (Deposition Exhibit 16 marked for</p> <p>2 identification.)</p> <p>3 Q. (BY MR. JAMES) And, Dr. Smith, just --</p> <p>4 just to make sure we're framed correctly here, my</p> <p>5 question to you is: How you would -- how would you</p> <p>6 characterize an odds ratio of 1.3?</p> <p>7 MS. O'DELL: Objection to form.</p> <p>8 A. Depends on what the confidence intervals</p> <p>9 are, but it's -- it reflects a 30 percent increase</p> <p>10 in whatever you're measuring.</p> <p>11 Q. (BY MR. JAMES) Would you characterize the</p> <p>12 association as weak?</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 A. 30 percent. It's relative. 30 percent</p> <p>15 more ovarian cancer is not weak. It's fatal.</p> <p>16 Q. (BY MR. JAMES) That's not the question</p> <p>17 that I asked.</p> <p>18 The question I asked is --</p> <p>19 A. I wouldn't call it weak.</p> <p>20 MS. O'DELL: Excuse me. Sorry.</p> <p>21 THE WITNESS: Sorry.</p> <p>22 MS. O'DELL: Let him finish and let me</p> <p>23 object. Go ahead.</p> <p>24 Q. (BY MR. JAMES) How would you characterize</p>
<p style="text-align: right;">Page 175</p> <p>1 Dr. Smith, the meta-analysis odds ratio for this</p> <p>2 paper is -- the crude odds ratio is 1.3, correct?</p> <p>3 MS. O'DELL: Objection to form.</p> <p>4 A. Yes, but it says "all studies."</p> <p>5 THE WITNESS: Do you want to pull this</p> <p>6 out --</p> <p>7 MS. O'DELL: Um-hum.</p> <p>8 THE WITNESS: -- so I can --</p> <p>9 MS. O'DELL: Sure.</p> <p>10 THE WITNESS: -- look at it?</p> <p>11 MR. JAMES: Leigh, I probably have it</p> <p>12 as well.</p> <p>13 Did you beat me to it?</p> <p>14 THE WITNESS: Yep. Well, she did. I</p> <p>15 didn't.</p> <p>16 MS. O'DELL: I was trying to redeem</p> <p>17 myself from not alphabetizing correctly before.</p> <p>18 Do you want to mark it, and I'll --</p> <p>19 MR. JAMES: Sure.</p> <p>20 BY MS. O'DELL: -- have to hand it to</p> <p>21 her.</p> <p>22 MR. JAMES: I'm gonna mark the</p> <p>23 Harlow '92 study as Exhibit 16.</p> <p>24 A. Let me go to this one. Easier for --</p>	<p style="text-align: right;">Page 177</p> <p>1 the 1.3, please?</p> <p>2 A. 30 percent.</p> <p>3 Q. Would you characterize it as a strong</p> <p>4 association?</p> <p>5 A. I would characterize it as statistically</p> <p>6 significant number.</p> <p>7 Q. Would you characterize it as a modest</p> <p>8 association?</p> <p>9 A. Modest, weak suggests unimportant, and I</p> <p>10 would not call it unimportant.</p> <p>11 Q. Do you understand that the authors of this</p> <p>12 paper use the terminology "modest"?</p> <p>13 A. Yes, they did.</p> <p>14 Q. Okay. Do you think that when they use</p> <p>15 that terminology they were calling it unimportant?</p> <p>16 A. I think that they suggested that it was</p> <p>17 small in size. Small increase, modest increase,</p> <p>18 that's what they were meaning.</p> <p>19 Q. And you understand one of the factors that</p> <p>20 experts use in evaluating an epidemiological body of</p> <p>21 literature is the strength of an association,</p> <p>22 correct?</p> <p>23 A. Yes.</p> <p>24 Q. And you discuss that later in your report,</p>

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<p>1 correct?</p> <p>2 A. I do.</p> <p>3 Q. And so my question here is whether, in</p> <p>4 your expert opinion, a 1.3 odds ratio can be</p> <p>5 characterized as strong, modest, weak, or another</p> <p>6 adjective?</p> <p>7 MS. O'DELL: Object to the form.</p> <p>8 A. I will use the authors term as modest.</p> <p>9 I'll accept that word.</p> <p>10 Q. (BY MR. JAMES) Would you also accept the</p> <p>11 terminology "weak," if the authors use that term?</p> <p>12 A. Did they use that term? Can you show me</p> <p>13 where they use the word "weak"?</p> <p>14 Q. You can turn to the last page. Usually</p> <p>15 I'm asking questions, but I'm happy to try to point</p> <p>16 you out to what I'm discussing. Page 26 of the</p> <p>17 Harlow paper.</p> <p>18 A. Um-hum.</p> <p>19 Q. Okay. Do you see the last paragraph</p> <p>20 there?</p> <p>21 A. Yes.</p> <p>22 Q. That first sentence?</p> <p>23 A. Oh, they did use the word "weak." If the</p> <p>24 authors use it, I will quote them.</p>	<p>1 Q. Okay. And here you note in the report, if</p> <p>2 you turn the page, Dr. Smith, you have copied in a</p> <p>3 table from the article, correct?</p> <p>4 A. Correct.</p> <p>5 Q. In here, we see that according to your</p> <p>6 report the odds ratio is a 1.29, correct?</p> <p>7 A. It is.</p> <p>8 Q. And, again, how would you characterize a</p> <p>9 1.29 odds ratio?</p> <p>10 A. A 29 percent increase in ovarian cancer</p> <p>11 after talc exposure.</p> <p>12 Q. And would you characterize that</p> <p>13 association as strong, modest, weak, or another</p> <p>14 adjective?</p> <p>15 MS. O'DELL: Object to the form.</p> <p>16 A. Are those my only choices?</p> <p>17 Q. (BY MR. JAMES) No, I gave you another</p> <p>18 adjective choice at the end of my question.</p> <p>19 MS. O'DELL: Objection.</p> <p>20 A. You gave me strong, modest, weak.</p> <p>21 Q. (BY MR. JAMES) I'm sorry if I -- maybe I</p> <p>22 misspoke, but I'm just asking you if you'd</p> <p>23 characterize a 1.29 as strong, modest, weak, or</p> <p>24 choose another adjective if you'd like.</p>
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<p>1 Q. Will you accept that terminology to</p> <p>2 describe the 1.3?</p> <p>3 MS. O'DELL: Object to the form.</p> <p>4 A. I -- in light of the larger body that's</p> <p>5 coming up, I will not accept that.</p> <p>6 Q. (BY MR. JAMES) You --</p> <p>7 A. That's my personal opinion.</p> <p>8 Q. Is your personal opinion guided by</p> <p>9 principles of epidemiology?</p> <p>10 MS. O'DELL: Objection to form.</p> <p>11 A. Yeah, I think so.</p> <p>12 Q. (BY MR. JAMES) You disagree with the</p> <p>13 characterization of the association by the authors</p> <p>14 of the study that you cite, correct?</p> <p>15 MS. O'DELL: Objection; asked and</p> <p>16 answered.</p> <p>17 A. Happens, yes.</p> <p>18 Q. (BY MR. JAMES) Okay. Dr. Smith, looking</p> <p>19 at your report, returning to the second study that</p> <p>20 you cite, you cite the Gross and Berg study; is that</p> <p>21 correct?</p> <p>22 A. I do.</p> <p>23 Q. That's from 1995, correct?</p> <p>24 A. It is.</p>	<p>1 MS. O'DELL: Object -- excuse me.</p> <p>2 Object to form.</p> <p>3 A. Statistically significant.</p> <p>4 Q. (BY MR. JAMES) Would you acknowledge that</p> <p>5 there are statistically significant associations</p> <p>6 that in epidemiological community would be referred</p> <p>7 to as weak?</p> <p>8 MS. O'DELL: Object to the form.</p> <p>9 A. The rate of dissolution of an aspirin</p> <p>10 tablet in the stomach, coated or noncoated, in terms</p> <p>11 of time to analgesia may be statistically</p> <p>12 significantly different if there's a 30 second</p> <p>13 difference between coated and noncoated.</p> <p>14 But that is a statistical significant</p> <p>15 difference that I find is not clinically</p> <p>16 significant. Whether your headache goes away</p> <p>17 30 seconds sooner or later isn't clinically</p> <p>18 significant to me; whereas, a 29 percent increase</p> <p>19 risk of ovarian cancer is very clinically</p> <p>20 significant to me.</p> <p>21 Q. (BY MR. JAMES) Do you understand that</p> <p>22 epidemiologists judge odds ratios based upon their</p> <p>23 strength?</p> <p>24 MS. O'DELL: Object to the form.</p>

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<p>1 A. They may use adjectives to quantitate the</p> <p>2 amount of difference in terms of size or strength</p> <p>3 and they may use words "modest." I understand they</p> <p>4 do that.</p> <p>5 Q. Do you understand --</p> <p>6 MS. O'DELL: Excuse me.</p> <p>7 Are -- I'm sorry. Are you finished,</p> <p>8 Dr. Smith?</p> <p>9 THE WITNESS: Yes.</p> <p>10 Q. (BY MR. JAMES) Do you understand that in</p> <p>11 judging associations, epidemiologists -- do you have</p> <p>12 expertise in epidemiology, Dr. Smith?</p> <p>13 A. I do not.</p> <p>14 Q. You do not?</p> <p>15 A. Just reading them; not doing them.</p> <p>16 Q. Do you understand that the weaker an odds</p> <p>17 ratio for an epidemiologist, that that bears some</p> <p>18 significance to an epidemiologist in making a causal</p> <p>19 conclusion?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A. It is one of Bradford Hill's nine factors</p> <p>22 or pos- -- he did -- didn't want to call them</p> <p>23 postulates.</p> <p>24 One of Bradford Hill -- I forget the</p>	<p>1 Q. (BY MR. JAMES) All right. The next study</p> <p>2 you discuss. And we're still on page 10, Dr. Smith,</p> <p>3 is the Cramer 1999 study.</p> <p>4 A. Yes.</p> <p>5 Q. And, I believe, just like with the prior,</p> <p>6 you have copied in a table from that study, right?</p> <p>7 A. Once you learn it on the computer, you</p> <p>8 just keep doing it.</p> <p>9 Q. Sure. And do you see there with the table</p> <p>10 that you've inputted into your report the odds</p> <p>11 ratio, a summary odds ratio of 1.4; is that right?</p> <p>12 A. I do.</p> <p>13 Q. Again, if the authors referred to that</p> <p>14 association in the paper as a relatively weak odds</p> <p>15 ratio, would you accept their terminology?</p> <p>16 MS. O'DELL: Do you happen to have</p> <p>17 that paper handy?</p> <p>18 THE WITNESS: You seem to be getting</p> <p>19 there faster than we are.</p> <p>20 I'm missing 14. Where did 14 go?</p> <p>21 Q. (BY MR. JAMES) I'll mark it as Exhibit --</p> <p>22 I think we're at 17?</p> <p>23 (Deposition Exhibit 17 marked for</p> <p>24 identification.)</p>
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<p>1 word he used -- nine factors in assessing causation</p> <p>2 and significance of epidemiologic findings.</p> <p>3 Q. (BY MR. JAMES) Do you agree that when an</p> <p>4 association is lower, weaker, smaller, or more</p> <p>5 modest, that the smaller, weaker, or more modest</p> <p>6 that it gets, even if it's statistically</p> <p>7 significant, the lower the odds ratio becomes the</p> <p>8 more concerned you become as an epidemiologist or as</p> <p>9 an expert with whether that association is due to</p> <p>10 chance, bias, confounding?</p> <p>11 MS. O'DELL: Obj- --</p> <p>12 Q. (BY MR. JAMES) Do you accept that?</p> <p>13 MS. O'DELL: Excuse me. Objection to</p> <p>14 the form.</p> <p>15 A. It depends. It depends on if this is a</p> <p>16 single study, a small-numbered study, or whether</p> <p>17 that small result is consistent, reproducible over a</p> <p>18 wide number of studies.</p> <p>19 Q. (BY MR. JAMES) Would you agree that the</p> <p>20 smaller the association the more concern there is --</p> <p>21 there -- there is with confounding, chance, or bias?</p> <p>22 MS. O'DELL: Excuse me. Objection;</p> <p>23 asked and answered.</p> <p>24 A. Not necessarily.</p>	<p>1 THE WITNESS: Are you get -- are you</p> <p>2 going -- I'm missing some of your exhibits.</p> <p>3 MS. O'DELL: We'll -- we'll straighten</p> <p>4 it out.</p> <p>5 THE WITNESS: Okay. I'm not</p> <p>6 responsible for that?</p> <p>7 MS. O'DELL: You are not responsible.</p> <p>8 THE WITNESS: Okay. I will quit</p> <p>9 worrying about it.</p> <p>10 And I dropped my mike. I'm sorry.</p> <p>11 Can you still hear me, sir?</p> <p>12 THE VIDEOGRAPHER: I can hear you.</p> <p>13 THE WITNESS: Okay.</p> <p>14 A. Yes, he does use "the relatively weak odds</p> <p>15 ratio observed."</p> <p>16 Q. (BY MR. JAMES) Would you agree with that</p> <p>17 conclusion in the study that you cite?</p> <p>18 A. As an epidemiologist, I think he's using</p> <p>19 epidemiologist speak. It's not my word choice.</p> <p>20 Q. You are here evaluating a body of</p> <p>21 epidemiologic literature, correct?</p> <p>22 A. I am. As a clinician and expert on</p> <p>23 ovarian cancer.</p> <p>24 Q. And do you see here where the authors of</p>

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<p style="text-align: right;">Page 186</p> <p>1 this article that you cited say in that same</p> <p>2 paragraph, quote, "Despite the consistency noted</p> <p>3 above, the relatively weak odds ratio observed could</p> <p>4 reflect potential biases, especially recall and</p> <p>5 confounding"?</p> <p>6 A. Yes. And then they go on to say:</p> <p>7 (Paraphrasing.) Recall bias seems more likely to</p> <p>8 affect exposures that occurred over a short period</p> <p>9 of time than those occurred long ago. The average</p> <p>10 duration of talc exceeded 20 years in both cases,</p> <p>11 genital talc exposure may be less likely to be</p> <p>12 subject to recall bias.</p> <p>13 And I cite that exact thing in</p> <p>14 quotations in my report. It is restated on</p> <p>15 page 356, I believe.</p> <p>16 Q. So that you cite the portion of the</p> <p>17 statement that you read, correct?</p> <p>18 A. Correct.</p> <p>19 Q. Okay. But you didn't cite the statement</p> <p>20 that I read into the record, correct?</p> <p>21 MS. O'DELL: Object to the form.</p> <p>22 A. Correct.</p> <p>23 Q. (BY MR. JAMES) Did you cite the portion</p> <p>24 of this -- of the article that supports your</p>	<p style="text-align: right;">Page 188</p> <p>1 response in your report?</p> <p>2 A. (Examined exhibit.) He -- I do not</p> <p>3 discuss it in my report. He himself called</p> <p>4 dose-response relationship, quote, "weak," unquote.</p> <p>5 Q. And you would agree that's an important</p> <p>6 finding of the study, correct?</p> <p>7 A. I think you ought to look at every study</p> <p>8 to see if it has a dose-response relationship.</p> <p>9 Q. Including this one, correct?</p> <p>10 A. Every study. Yes, including this one.</p> <p>11 Q. All right. Next, Dr. Smith, you discuss</p> <p>12 the Huncharek study, correct?</p> <p>13 A. Correct.</p> <p>14 Q. And in the text --</p> <p>15 THE WITNESS: Are you just going to</p> <p>16 supply that to us?</p> <p>17 MR. JAMES: I can or the --</p> <p>18 THE WITNESS: I'd like to have the</p> <p>19 studies as we discuss them, if you wouldn't mind.</p> <p>20 MR. JAMES: Absolutely. And --</p> <p>21 absolutely.</p> <p>22 And right now, I'm looking at your</p> <p>23 report with you as well, so . . .</p> <p>24 THE WITNESS: Sure. Sure. But they</p>
<p style="text-align: right;">Page 187</p> <p>1 opinion?</p> <p>2 MS. O'DELL: Objection to the form.</p> <p>3 A. I sub- -- quoted the part of the paper</p> <p>4 where the author specifically addressed concerns</p> <p>5 about recall, bias, and found them unlikely. I</p> <p>6 think it's important that he thought of it. I think</p> <p>7 it's real important that he thought of it.</p> <p>8 But I think he, and every author, in</p> <p>9 every study should go through his or her study with</p> <p>10 a fine-tune comb that says "What -- "Why should I</p> <p>11 believe these results?</p> <p>12 "What could I -- how -- what could I</p> <p>13 have made a mistake?</p> <p>14 "What are confounding factors?</p> <p>15 "Where is the bias that could've been</p> <p>16 introduced?</p> <p>17 "Did I draw my conclusion from the</p> <p>18 data in my study?"</p> <p>19 That's what every good author does,</p> <p>20 and so he did that. And then he answered his own</p> <p>21 question, "No, I don't think that's a confounding</p> <p>22 factor."</p> <p>23 Q. (BY MR. JAMES) In discussing this study,</p> <p>24 do you discuss Dr. Cramer's findings on dose</p>	<p style="text-align: right;">Page 189</p> <p>1 have -- I -- mine is a summary. You got the real</p> <p>2 thing.</p> <p>3 MR. JAMES: Sure. As do you. But I'm</p> <p>4 happy to give you my copy.</p> <p>5 THE WITNESS: Well, Ms. O'Dell does</p> <p>6 not mind getting every study for us. She's . . .</p> <p>7 MR. JAMES: All right. So I'm going</p> <p>8 to mark the Huncharek study as Exhibit Number 18.</p> <p>9 (Deposition Exhibit 18 marked for</p> <p>10 identification.)</p> <p>11 A. Thank you. (Examined exhibit.)</p> <p>12 Q. (BY MR. JAMES) And you note in your</p> <p>13 report an odds ratio of 1.33, correct?</p> <p>14 A. Yes. Ever versus never exposure,</p> <p>15 "Relative risk of 1.33 with a 95% confidence</p> <p>16 interval of 1.16 to 1.45, a statistically</p> <p>17 significant result suggesting a 33% increased risk</p> <p>18 of ovarian cancer." That is a quote from the study.</p> <p>19 Q. Dr. Smith, would -- how would you</p> <p>20 characterize a 1.33 odds ratio?</p> <p>21 A. 33 percent --</p> <p>22 Q. Okay. And would --</p> <p>23 A. -- clinically significant, statistically</p> <p>24 significant.</p>

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<p>1 Q. You recognize that all statistically</p> <p>2 significant associations cannot be described as</p> <p>3 strong, correct?</p> <p>4 A. No. We've been through this.</p> <p>5 MS. O'DELL: Objection to form.</p> <p>6 A. Not all statistical significant -- you</p> <p>7 used the word "strong." I used the word "clinically</p> <p>8 significant." Those are different things.</p> <p>9 Q. (BY MR. JAMES) I agree with you. And I'm</p> <p>10 asking you about strength.</p> <p>11 MS. O'DELL: Could you repeat your</p> <p>12 question, please?</p> <p>13 MR. JAMES: I'd be happy to.</p> <p>14 Q. (BY MR. JAMES) Would you characterize the</p> <p>15 odds ratio in this paper as strong, modest, weak or</p> <p>16 another adjective that you prefer?</p> <p>17 MS. O'DELL: Object to the form; asked</p> <p>18 and answered.</p> <p>19 MR. JAMES: It hasn't been asked.</p> <p>20 A. Clinically, statistically significant.</p> <p>21 That's the word I'm gonna use.</p> <p>22 Q. (BY MR. JAMES) Is there a reason why</p> <p>23 you're uncomfortable characterizing the odds ratio</p> <p>24 with one of the adjectives strong --</p>	<p>1 there as dose response in the above sentence.</p> <p>2 Do you see where I've --</p> <p>3 A. Yes.</p> <p>4 Q. -- read that?</p> <p>5 A. Yes.</p> <p>6 Q. Okay. And what's your basis for that</p> <p>7 statement?</p> <p>8 A. This is -- I believe this is an ever/never</p> <p>9 study. Now, have you -- so if it's ever/never, you</p> <p>10 didn't use it or you ever used it. And so you --</p> <p>11 implicitly, you can't get dose response if you don't</p> <p>12 look at frequency and duration. And a lot of these</p> <p>13 talc studies are ever/never.</p> <p>14 Q. And this is not an attempt for a gotcha or</p> <p>15 anything like that, but I want to make sure we're</p> <p>16 looking at the same paper.</p> <p>17 So can you turn with me to page 1958?</p> <p>18 A. (Complied.)</p> <p>19 Q. And you see Table 2. There's a table</p> <p>20 there with dose response data.</p> <p>21 A. (Examined exhibit.) Well . . .</p> <p>22 Q. Do you see here that the --</p> <p>23 A. Yeah, I see --</p> <p>24 Q. I'm sorry.</p>
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<p>1 A. That, yeah --</p> <p>2 Q. -- modest or weak?</p> <p>3 A. -- epidemiologists use because weak in --</p> <p>4 I'm not an epidemiologist. Perhaps I don't have the</p> <p>5 epidemiologic --</p> <p>6 (Counsel conferring off the record.)</p> <p>7 A. Do you want me to wait while y'all talk?</p> <p>8 Q. (BY MR. JAMES) No, ma'am.</p> <p>9 A. I don't know the connotations of what</p> <p>10 "weak" means in epidemiologic circles. If it just</p> <p>11 means a small number, less than 2.0, weak, in my</p> <p>12 medical clinical brain implies unimportant, trivial.</p> <p>13 And I think that kind of difference, when you talk</p> <p>14 about ovarian cancer, is not trivial and it's not</p> <p>15 unimportant.</p> <p>16 So maybe that's my hang-up, and maybe</p> <p>17 it's because I'm not an epidemiologist. I'm a -- I</p> <p>18 am person who takes care -- or took care of patients</p> <p>19 with ovarian -- continues to take care of people</p> <p>20 with ovarian cancer.</p> <p>21 Q. You include the statement in your report</p> <p>22 that "The study" -- and I'm looking at your report</p> <p>23 now -- "did not collect the necessary data to permit</p> <p>24 this determination," in what you're referring to</p>	<p>1 A. -- I see your table.</p> <p>2 Q. Thank you.</p> <p>3 A. I see your table. Here it's used. And I</p> <p>4 see what I wrote, and I haven't reread this</p> <p>5 immediately prior to my deposition.</p> <p>6 MS. O'DELL: And if you need a few</p> <p>7 minutes to refresh yourself, Dr. Smith, feel free to</p> <p>8 do that.</p> <p>9 THE WITNESS: I hate to waste your</p> <p>10 time, but I'd like to do that.</p> <p>11 MS. O'DELL: Yes, please.</p> <p>12 MR. JAMES: Yeah. Can we go off the</p> <p>13 record while the Doctor reviews the paper?</p> <p>14 THE WITNESS: Sure.</p> <p>15 MR. JAMES: Leigh, Margaret, is that</p> <p>16 fine?</p> <p>17 MS. O'DELL: You know, if it's gonna</p> <p>18 take you a few minutes, I think --</p> <p>19 THE WITNESS: Yeah.</p> <p>20 MS. O'DELL: -- we'll go off. If it's</p> <p>21 gonna take you a minute or so, let's just give the</p> <p>22 Doctor a moment and we'll keep going.</p> <p>23 THE VIDEOGRAPHER: Going off the</p> <p>24 record. The time is 2:44 p.m.</p>

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<p>1 (A recess was taken from 2:44 p.m. 2 to 2:56 p.m.) 3 THE VIDEOGRAPHER: This marks the 4 beginning of Disk 3. Back on the record. The time 5 is 2:56 p.m. 6 Q. (BY MR. JAMES) Dr. Smith, you've had a 7 chance to look at the Huncharek paper, correct? 8 A. I have. 9 Q. And does that paper include data to permit 10 a conclusion as to dose response? 11 A. It does not. 12 Q. And what's your basis for that statement? 13 A. They only had dose response information 14 on 9 of the 16 studies, and the authors themselves 15 said only a small minority of studies contain dose 16 responses. 17 This is on page 1958, the left side 18 column, second paragraph that starts there about 19 halfway -- between one-third and one-half way down. 20 "Unfortunately, only limited data were 21 available and only a small minority of" -- oh, I 22 lost my place -- "only a small minority" -- 23 UNIDENTIFIED SPEAKER: (Inaudible.) 24 THE WITNESS: Okay.</p>	<p>1 must not be understanding you. 2 Q. Are you misunderstanding the paper? 3 MS. O'DELL: Objection to form. 4 A. No. 5 MS. O'DELL: She said she was 6 misunderstanding your question. 7 MR. JAMES: I'm posing the questions, 8 Leigh. Thank you. 9 Q. (BY MR. JAMES) Dr. Smith, you've stated 10 in your report that, quote, "The study did not 11 collect the necessary data to permit this 12 determination," close quote. 13 Do you see that? 14 A. Yes. 15 Q. And your position is that the 16 dose-response findings in this paper are a nullity? 17 Is that your position? 18 MS. O'DELL: Object to the form. 19 A. I don't know what you mean by "nullity," 20 but they didn't have sufficient data to determine a 21 clear dose response. 22 Q. (BY MR. JAMES) Okay. And yet we do see 23 here that the authors have made a conclusion about 24 dose response, correct?</p>
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<p>1 A. -- "only a small minority of studies 2 contain dose-response information of any type 3 and (2), substantial differences existed in dose 4 stratification levels among the studies reporting 5 such information. It is therefore not possible to 6 perform more sophisticated modeling of dose response 7 data." 8 Final -- far- -- farther down on that, 9 "The lowest half exposure category in this Cramer 10 study was 'less than 30' applications, which is not 11 consistent with other 'low.'" 12 "Taken together, these" -- last 13 sentence, "Taken together, these data show a lack of 14 clear dose-response relationship." Okay. 15 Q. (BY MR. JAMES) So you concluded your 16 answer to my question with a sentence in the paper 17 that says, quote, "Taken together, these data show a 18 lack of a clear dose-response relationship," close 19 quote, correct? 20 A. Correct. 21 MS. O'DELL: Object to the form. 22 Q. (BY MR. JAMES) So the authors have made 23 conclusions about dose response, correct? 24 A. They can't. They said they couldn't. I</p>	<p>1 MS. O'DELL: Object to the form. 2 A. "Despite the findings, the data showed a 3 lack of clear dose-response relationship, making the 4 relative risk of questionable validity." That's in 5 their abstract. 6 So I don't see where they say they 7 have made a clear dose-response relationship. 8 Q. (BY MR. JAMES) Okay. Let's just let the 9 language of the paper speak for itself and we can 10 move on. 11 MS. O'DELL: Object to the form. 12 Q. (BY MR. JAMES) Next you discuss the 13 Langseth study, correct? 14 A. Yes, sir. 15 Q. And on page 12 of your report, you quote 16 the statement in the paper, and I'm gonna mark it as 17 Exhibit Number 19. 18 (Deposition Exhibit 19 marked for 19 identification.) 20 Q. (BY MR. JAMES) Okay. I'm handing you a 21 clean copy of Exhibit Number 19 of Langseth. 22 A. Thank you. 23 Q. Okay. In your report you quote the 24 article for the proposition --</p>

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<p>1 A. You gave me two copies.</p> <p>2 THE WITNESS: Does somebody else need</p> <p>3 another one?</p> <p>4 Q. (BY MR. JAMES) -- for the proposition</p> <p>5 that the epide- -- "epidemiological evidence</p> <p>6 suggests that the use of cosmetic talc in the</p> <p>7 perineal area may be associated with ovarian cancer</p> <p>8 risk."</p> <p>9 That's what you quote in your report,</p> <p>10 correct?</p> <p>11 A. Correct.</p> <p>12 Q. If you look at the second page of the</p> <p>13 article in the section titled "Proposal: To Research</p> <p>14 Community," do you see where I am?</p> <p>15 A. I do.</p> <p>16 Q. Okay. The authors there state, quote,</p> <p>17 "The current body of experimental and</p> <p>18 epidemiological evidence is insufficient to</p> <p>19 establish a causal association between perineal use</p> <p>20 of talc and ovarian cancer risk," close quote.</p> <p>21 Do you see where I read that?</p> <p>22 A. I do.</p> <p>23 Q. And that conclusion of the author -- or</p> <p>24 the authors is not included in your report, is it?</p>	<p>1 Q. Sorry.</p> <p>2 A. -- cite that.</p> <p>3 Q. And, again, you -- in your report, you</p> <p>4 concluded that meta-analyses are -- I think you used</p> <p>5 the terminology "most valid" way to look at this</p> <p>6 issue; is that right?</p> <p>7 A. Okay. I think they're the best we have,</p> <p>8 and I think they are the best we are going to have.</p> <p>9 The best studies to determine</p> <p>10 causation are randomized, controlled, prospective</p> <p>11 trials, and more than one of them. That's what's</p> <p>12 called Level 1 evidence.</p> <p>13 There is no ethical way we can apply</p> <p>14 any possible carcinogen, suspected carcinogen,</p> <p>15 proven carcinogen to the perineum of any woman and</p> <p>16 have that be ethically acceptable. That study</p> <p>17 cannot be done.</p> <p>18 We are going to have to validate the</p> <p>19 epidemiologic data in the laboratory, because that's</p> <p>20 the only ethical place.</p> <p>21 Q. And you understand the length of study is</p> <p>22 authored by the IARC Working Group, correct?</p> <p>23 A. Yes.</p> <p>24 Q. And do you understand that IARC has</p>
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<p>1 MS. O'DELL: Object to the form.</p> <p>2 A. It is not. I don't agree with that</p> <p>3 conclusion.</p> <p>4 Q. (BY MR. JAMES) So this is another paper</p> <p>5 that you've cited where you disagree with the</p> <p>6 authors' conclusions, correct?</p> <p>7 A. Correct. They have a statistically</p> <p>8 significant overall risk of 1.35 -- between 1.26</p> <p>9 to 1.46, so that is -- and then it says on research</p> <p>10 report what this study shows, "Epidemiologic [sic]</p> <p>11 evidence suggests the use of cosmetic talc in the</p> <p>12 perineal area may be associated with ovarian cancer</p> <p>13 risk."</p> <p>14 Q. That's the portion that you've cited in</p> <p>15 your report, correct?</p> <p>16 A. Yes, that is exactly what I quoted.</p> <p>17 Q. But you didn't quote the sentence that I</p> <p>18 read that specifically disclaims a causal</p> <p>19 association, correct?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 Q. (BY MR. JAMES) Or --</p> <p>22 A. I --</p> <p>23 Q. Well, let me --</p> <p>24 A. I did not --</p>	<p>1 classifi- -- classified perineal talc application as</p> <p>2 a 2B?</p> <p>3 MS. O'DELL: Objection to --</p> <p>4 Q. (BY MR. JAMES) Do you understand that?</p> <p>5 MS. O'DELL: Excuse me. Object to the</p> <p>6 characteration -- characterization regarding the</p> <p>7 working group.</p> <p>8 A. IARC 93 classified talc as a 2B possible</p> <p>9 carcinogen.</p> <p>10 Q. (BY MR. JAMES) Do you understand IARC has</p> <p>11 not classified talc as a carcinogen, correct?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A. Correct.</p> <p>14 Q. (BY MR. JAMES) And IARC has not</p> <p>15 classified talc as a probable carcinogen, correct?</p> <p>16 A. Correct.</p> <p>17 Q. The conclusion that you're offering -- the</p> <p>18 opinion that you're offering here today conflicts</p> <p>19 with the IARC 2B finding, correct?</p> <p>20 MS. O'DELL: Objection to form.</p> <p>21 A. I told you that a study can't apply</p> <p>22 anything that's a possible, and I didn't say talc in</p> <p>23 any study.</p> <p>24 I said the model for a randomized</p>

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<p>1 controlled trial would be apply whatever substance</p> <p>2 you want to women and see if they result in this</p> <p>3 disease.</p> <p>4 But if you start with a possible,</p> <p>5 probable, or absolutely carcinogen, you're never</p> <p>6 gonna -- you can't -- you can't even write that down</p> <p>7 on the paper. That's not going anywhere.</p> <p>8 That study will -- multiple studies we</p> <p>9 need -- we needed to have to have Level 1 evidence</p> <p>10 will never be done.</p> <p>11 Q. (BY MR. JAMES) And I think that your</p> <p>12 answer maybe wasn't responsive to my question.</p> <p>13 And so my question is whether the</p> <p>14 causation opinion you're offering in this litigation</p> <p>15 is different than the conclusion reached by IARC?</p> <p>16 A. IARC in -- based on data up to 2006,</p> <p>17 declared talc a 2B possible carcinogen.</p> <p>18 I believe that since 2006, in the past</p> <p>19 12 years, we have a plethora of data that leads me</p> <p>20 to the conclusion that talc is a Class 1 carcinogen.</p> <p>21 Q. You know IARC has not, to date, made that</p> <p>22 classification, correct?</p> <p>23 A. That's right.</p> <p>24 Q. Okay. Next in your report you discuss a</p>	<p>1 A. We've had this discussion before.</p> <p>2 Q. Okay. Fair enough.</p> <p>3 And your answers prior hold here as</p> <p>4 well?</p> <p>5 A. They hold.</p> <p>6 Q. Understood.</p> <p>7 In your report, I didn't see any</p> <p>8 discussion in the -- when you're mentioning the</p> <p>9 Terry paper of the paper's findings on dose</p> <p>10 response.</p> <p>11 Are you familiar with the</p> <p>12 dose-response findings in the Terry paper?</p> <p>13 A. Once more, I'll need a moment to look.</p> <p>14 (Examined exhibit.) They did -- there</p> <p>15 is no significant trend for increasing number of</p> <p>16 lifetime applications.</p> <p>17 Q. And if you see on page -- I think you're</p> <p>18 reading on page 817; is that right, Dr. Smith?</p> <p>19 A. I was reading from the abstracts.</p> <p>20 Q. Oh, yes, Doctor.</p> <p>21 If we also look at the page 812.</p> <p>22 A. (Complied.)</p> <p>23 Q. Do you see there where they say "Evidence</p> <p>24 for a dose-response relationship has been</p>
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<p>1 Terry pooled analysis, correct?</p> <p>2 A. Yes.</p> <p>3 Q. And, again, here in your report -- and we</p> <p>4 can mark Terry if that -- I'll hand you a copy of</p> <p>5 that.</p> <p>6 In your report you note the overall</p> <p>7 odds ratio in Terry is a 1.24, correct?</p> <p>8 A. Yes.</p> <p>9 Q. Okay. And I'm gonna mark Terry as Exhibit</p> <p>10 Number 20.</p> <p>11 (Deposition Exhibit 20 marked for</p> <p>12 identification.)</p> <p>13 Q. (BY MR. JAMES) You see here that the</p> <p>14 Terry odds ratio of 1.24 is lower than some of the</p> <p>15 odds ratios reported in the prior meta-analyses,</p> <p>16 correct?</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 A. Slightly. Well, let's see.</p> <p>19 (Examined exhibit.) 1.33. 1.24 is</p> <p>20 smaller. Yes, I agree with -- that 1.24 is lower</p> <p>21 than 1.33.</p> <p>22 Q. (BY MR. JAMES) Would you agree with the</p> <p>23 authors of this paper when they describe the odds</p> <p>24 ratio as a modest odds ratio?</p>	<p>1 inconsistent" or are you on another page?</p> <p>2 A. Did you say 812?</p> <p>3 Q. Yes, Doctor.</p> <p>4 A. The top?</p> <p>5 Q. Yes, The top.</p> <p>6 A. Yes. "Evidence of dose-response</p> <p>7 relationship has been inconsistent."</p> <p>8 Q. And is there a reason why you don't</p> <p>9 discuss the dose-response findings of Terry in your</p> <p>10 report?</p> <p>11 A. Because they didn't use -- they didn't</p> <p>12 observe the trend of increased risk applications. I</p> <p>13 mean, I -- it wasn't a pointed omission.</p> <p>14 MS. O'DELL: If you want to re- --</p> <p>15 need to review the paper.</p> <p>16 Q. (BY MR. JAMES) Dr. Smith, are you</p> <p>17 reviewing or may I continue with another question?</p> <p>18 A. Hold on one second. (Examined exhibit.)</p> <p>19 Q. Sure.</p> <p>20 A. (Paraphrasing.) No trend in cumulative</p> <p>21 use was evident in analyses restricted to ever-users</p> <p>22 of genital powder. Taken together, these</p> <p>23 observations suggest that the significant trend test</p> <p>24 largely reflects ever/never.</p>

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<p>1 I would -- I would suggest that I</p> <p>2 didn't mention a negative. I mean, it isn't there.</p> <p>3 Q. So that if a paper finds that there's no</p> <p>4 dose response, that's the basis for you not to</p> <p>5 report that finding?</p> <p>6 MS. O'DELL: Object to the form.</p> <p>7 A. I think it didn't add anything to the body</p> <p>8 of this report.</p> <p>9 Q. (BY MR. JAMES) You acknowledge later in</p> <p>10 your report that whether or not the literature</p> <p>11 reports a dose response, one way or the other, is</p> <p>12 important to the causative analysis, correct?</p> <p>13 A. I accept that it -- I could have improved</p> <p>14 my report by including that negative information.</p> <p>15 Q. And if you look at the page 820 of the</p> <p>16 Terry article -- it's at the very end of the</p> <p>17 article. We see in the language at the top of the</p> <p>18 right column that the authors conclude, quote, "More</p> <p>19 work is needed to understand how genital powders may</p> <p>20 exert a carcinogenic effect, and which constituents</p> <p>21 (e.g., talc) may be involved."</p> <p>22 MS. O'DELL: Object to form.</p> <p>23 A. I would agree with that wholeheartedly.</p> <p>24 Q. (BY MR. JAMES) So as of 2013, Dr. Smith,</p>	<p>1 ratio of the 1.25 is less than the overall odds</p> <p>2 ratio reported of the 1.31, correct?</p> <p>3 A. I --</p> <p>4 Q. And another -- maybe an easier place to</p> <p>5 reference, Dr. Smith, would be the abstract in the</p> <p>6 results section.</p> <p>7 A. No. I believe I used the serous invasion</p> <p>8 rather than all. And that -- that's just -- I</p> <p>9 should've put "serous carcinoma" there, not "all."</p> <p>10 That's just a flat out mistake.</p> <p>11 Q. And if we see in the Results section,</p> <p>12 Dr. Smith, we see -- and this is in the abstract</p> <p>13 portion of the paper, they report that the odds</p> <p>14 ratio with any perineal talc use associated with</p> <p>15 ovarian cancer --</p> <p>16 MS. O'DELL: Where -- where are you</p> <p>17 reading from?</p> <p>18 MR. JAMES: I'm in the abstract in the</p> <p>19 Results section.</p> <p>20 MS. O'DELL: Okay.</p> <p>21 MR. JAMES: This is 1.31.</p> <p>22 A. Yeah. That's just a typo. Yeah, 1.31 --</p> <p>23 Q. (BY MR. JAMES) And then --</p> <p>24 MS. O'DELL: Excuse me.</p>
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<p>1 the Terry authors are concluding that the --</p> <p>2 concluding that whether or not talc exerts a</p> <p>3 carcinogenic effect is undetermined, correct?</p> <p>4 MS. O'DELL: Object to the form;</p> <p>5 misstates the record.</p> <p>6 A. That's what they stated, exactly. And I</p> <p>7 would agree more work needs to be done.</p> <p>8 Q. (BY MR. JAMES) All right. Finally,</p> <p>9 Dr. Smith, you discuss the Penninkilampi --</p> <p>10 A. Yes.</p> <p>11 Q. -- study, correct?</p> <p>12 A. Yes.</p> <p>13 Q. I'm gonna mark the Penninkilampi study as</p> <p>14 Exhibit Number 21.</p> <p>15 (Deposition Exhibit 21 marked for</p> <p>16 identification.)</p> <p>17 Q. (BY MR. JAMES) In your report, Dr. Smith,</p> <p>18 you refer to the odds ratio with -- associated with</p> <p>19 long-term powder use as a 1.25, correct?</p> <p>20 A. Correct.</p> <p>21 Q. And if we look at Figure 2 of the study --</p> <p>22 or it's Table 2 --</p> <p>23 A. (Complied.)</p> <p>24 Q. -- you see that the long-term use odds</p>	<p>1 Q. (BY MR. JAMES) Let me finish.</p> <p>2 MS. O'DELL: Let him finish, please.</p> <p>3 A. I'm sorry.</p> <p>4 Q. (BY MR. JAMES) So the abstract reports</p> <p>5 that the overall odds ratio was a 1.31. But if you</p> <p>6 continue on reading in the abstract, you see that</p> <p>7 the long-term talc use odds ratio is a 1.25.</p> <p>8 Do you see that?</p> <p>9 MS. O'DELL: Object to the form.</p> <p>10 A. Okay. How far down did you go? I see</p> <p>11 "any," then "more than 3600 lifetime applications"</p> <p>12 is 1.42.</p> <p>13 And ever use is 1.35, 1.27, 1.43 in</p> <p>14 case control, but not cohort studies.</p> <p>15 Q. (BY MR. JAMES) Okay. And my apol- --</p> <p>16 A. "However" --</p> <p>17 Q. Oh, sorry, Doctor.</p> <p>18 A. -- is that where -- is that where you are?</p> <p>19 Is that the right sentence now?</p> <p>20 Q. If -- if I may. If I may refer you back</p> <p>21 to Figure 2 and not Table 2, I think that will get</p> <p>22 us there quicker.</p> <p>23 MS. O'DELL: I'm sorry, Scott. I'm</p> <p>24 sort of confused.</p>

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<p style="text-align: right;">Page 210</p> <p>1 MR. JAMES: Sure. And I'm gonna --</p> <p>2 I'm straightening this up right now.</p> <p>3 THE WITNESS: Okay. Okay.</p> <p>4 Q. (BY MR. JAMES) So we're looking at</p> <p>5 Figure 2, which is where I initially --</p> <p>6 A. Okay.</p> <p>7 Q. -- tried to get us.</p> <p>8 A. Okay. So -- okay. So the -- yes.</p> <p>9 MS. O'DELL: Okay. Excuse me. Let</p> <p>10 him --</p> <p>11 THE WITNESS: I'm sorry.</p> <p>12 MS. O'DELL: -- ask a question.</p> <p>13 Q. (BY MR. JAMES) So on page -- on</p> <p>14 Figure 2 --</p> <p>15 MS. O'DELL: Excuse me. Dr. Smith, if</p> <p>16 you'll let him ask the question.</p> <p>17 This is very -- gonna be very</p> <p>18 confusing on the record, so if we could just start</p> <p>19 over and make it clear.</p> <p>20 MR. JAMES: Sure. Sure.</p> <p>21 MS. O'DELL: Thank you.</p> <p>22 Q. (BY MR. JAMES) So we're looking at the</p> <p>23 Penninkilampi study, Figure 2, page 46, correct?</p> <p>24 A. Correct.</p>	<p style="text-align: right;">Page 212</p> <p>1 Q. (BY MR. JAMES) Uh-huh.</p> <p>2 A. Cramer's got a paper. I think it's Cramer</p> <p>3 has a paper that tubal ligation increases ovarian</p> <p>4 cancer risks in one of his forms. I mean, it's --</p> <p>5 you know, you have the outliers. But the body of</p> <p>6 literature doesn't support this single decrease from</p> <p>7 1.31 to 1.25. But, you know, okay, but I see it. I</p> <p>8 know it.</p> <p>9 Q. And in your report you discuss</p> <p>10 Penninkilampi as politically -- excuse me,</p> <p>11 particularly important to your analysis, correct?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A. I really like this study. I -- I like the</p> <p>14 scope of it. I like inclusion of the cohorts. It</p> <p>15 has a huge number of cases. Bigger is better. When</p> <p>16 you get away from small numbers and into the really</p> <p>17 large numbers, you have a much higher chance of</p> <p>18 finding truth if you -- so I like this study.</p> <p>19 Q. (BY MR. JAMES) Do you see on page 42 of</p> <p>20 the study, it's the left-hand column, top paragraph,</p> <p>21 bottom sentence, the authors state, "Hence, while</p> <p>22 perineal talc use has not been shown to be safe, in</p> <p>23 a similar regard, a certain causal link between talc</p> <p>24 use and ovarian cancer has not yet been</p>
<p style="text-align: right;">Page 211</p> <p>1 Q. Okay. And do we see here, which is where</p> <p>2 I was trying to go, that the "Any perineal talc use"</p> <p>3 odds ratio reported here is a 1.31, correct?</p> <p>4 A. Correct.</p> <p>5 Q. And then they go on in Figure 2 to state</p> <p>6 that the "Long-Term perineal talc use" odds ratio is</p> <p>7 a 1.25, correct?</p> <p>8 A. Correct.</p> <p>9 Q. And the authors also note that it's a</p> <p>10 lower magnitude odds ratio, correct?</p> <p>11 A. Correct.</p> <p>12 Q. Does that lower magnitude odds ratio for</p> <p>13 long-term perineal talc use comport with your</p> <p>14 litigation opinions?</p> <p>15 MS. O'DELL: Object to the form.</p> <p>16 A. It's not inconsistent.</p> <p>17 Q. (BY MR. JAMES) It's not inconsistent with</p> <p>18 your opinions that a long-term talc user has a lower</p> <p>19 odds ratio?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A. It is not unusual to have a -- a single</p> <p>22 inconsistent finding within one study. It doesn't</p> <p>23 change the whole picture of -- I mean, I note it. I</p> <p>24 acknowledge it.</p>	<p style="text-align: right;">Page 213</p> <p>1 established," close quote?</p> <p>2 A. They do say that.</p> <p>3 Q. Okay. Do you agree with that finding or</p> <p>4 statement?</p> <p>5 A. My conclusions are based on the totality</p> <p>6 of all the evidence that I have reviewed, not just</p> <p>7 the epidemiologic. Certainly, they have not reached</p> <p>8 that conclusion.</p> <p>9 MR. KLATT: Objection; nonresponsive.</p> <p>10 Q. (BY MR. JAMES) And the Penninkilampi</p> <p>11 authors did not reach a causation conclusion,</p> <p>12 correct?</p> <p>13 MS. O'DELL: Object to form.</p> <p>14 A. Well, in their introduction, they said a</p> <p>15 causal link has not been used.</p> <p>16 And their discussion is that they said</p> <p>17 that a (paraphrasing) talc use appears to be</p> <p>18 associated with an increased risk of serous ovarian</p> <p>19 cancer, both invasive and borderline, and not with</p> <p>20 mucinous and with endometrial -- endometrioid</p> <p>21 ovarian cancer with perineal use.</p> <p>22 Q. (BY MR. JAMES) The question remains,</p> <p>23 Dr. Smith: The Penninkilampi study that you cite as</p> <p>24 particularly important in your report, the authors</p>

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<p>1 there do not render the conclusion that talc is a</p> <p>2 demonstrated cause of ovarian cancer, do they?</p> <p>3 MS. O'DELL: Objection to form; asked</p> <p>4 and answered.</p> <p>5 A. They ask for a sustained need for further</p> <p>6 research on the potential mechanism by which ovarian</p> <p>7 cancer may be caused by talc.</p> <p>8 So they -- they do not allow a causal</p> <p>9 relationship, nor do they allow rejecting that</p> <p>10 causal relationship.</p> <p>11 Q. (BY MR. JAMES) And here, we do know that</p> <p>12 you have rendered the causation opinion, and so your</p> <p>13 causation opinion is different than the opinion</p> <p>14 reached by the authors of the Penninkilampi study,</p> <p>15 isn't it?</p> <p>16 A. Yes.</p> <p>17 Q. When evaluating the Penninkilampi study,</p> <p>18 did you note that the Penninkilampi authors omitted</p> <p>19 certain cohort data?</p> <p>20 A. They use Gertig rather than Gates.</p> <p>21 Q. Okay. And the Gates paper is the</p> <p>22 follow-up paper, correct?</p> <p>23 A. The Gates paper is the -- do you want to</p> <p>24 do the -- the prospective studies now or do you want</p>	<p>1 questions.</p> <p>2 MR. JAMES: Okay. So I'm marking the</p> <p>3 Gates 2010 paper as Exhibit 22.</p> <p>4 (Deposition Exhibit 22 marked for</p> <p>5 identification.)</p> <p>6 Q. (BY MR. JAMES) And so the question --</p> <p>7 I'll rephrase.</p> <p>8 MS. O'DELL: Oh. I thought you were</p> <p>9 gonna hand me something else. Okay.</p> <p>10 Q. (BY MR. JAMES) The Gates paper is the --</p> <p>11 is a paper produced on the Nurses' Health cohort,</p> <p>12 correct, Dr. Smith?</p> <p>13 A. Did you say the Gates' paper?</p> <p>14 Q. Yes.</p> <p>15 A. Yes.</p> <p>16 MS. O'DELL: Are you gonna mark</p> <p>17 Gertig, if you're gonna compare the two?</p> <p>18 MR. JAMES: I'll mark Gertig as</p> <p>19 Exhibit 23.</p> <p>20 (Deposition Exhibit 23 marked for</p> <p>21 identification.)</p> <p>22 Q. (BY MR. JAMES) And Dr. Smith, Gertig is</p> <p>23 also a Nurses' Health paper, correct?</p> <p>24 A. It's the first one.</p>
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<p>1 to do it as part of this?</p> <p>2 Q. I -- right now, I'd just like to continue</p> <p>3 with the questioning.</p> <p>4 A. Okay. Okay.</p> <p>5 Q. And if there is a --</p> <p>6 A. Okay.</p> <p>7 Q. -- point where you'd like the papers,</p> <p>8 we'll get them for you.</p> <p>9 A. Thank you.</p> <p>10 Q. Okay.</p> <p>11 A. I always love the papers.</p> <p>12 The Gates study is the first half of</p> <p>13 the Nurses' study.</p> <p>14 MS. O'DELL: Scott, if you're gonna</p> <p>15 mark the papers, why don't we go ahead and mark</p> <p>16 Gates and --</p> <p>17 THE WITNESS: Gertig?</p> <p>18 MS. O'DELL: -- if you're going to --</p> <p>19 Yes.</p> <p>20 If you're going to -- I think we've</p> <p>21 marked them --</p> <p>22 MR. JAMES: Sure. That sounds fine.</p> <p>23 MS. O'DELL: That way the Doctor can</p> <p>24 have it in front of her while she's answering the</p>	<p>1 Q. Thank you.</p> <p>2 A. Thank you.</p> <p>3 Q. All right. And so to reframe the</p> <p>4 question, Dr. Smith, the Penninkilampi study omits</p> <p>5 the data from the Gates 2010 study, correct?</p> <p>6 MS. O'DELL: Object to the form.</p> <p>7 Excuse me. I'm sorry.</p> <p>8 A. It used Gertig and not Gates.</p> <p>9 Q. (BY MR. JAMES) Okay. Is there --</p> <p>10 A. I -- I don't think he -- I don't know why</p> <p>11 he -- that is what it is.</p> <p>12 Q. And, again, you understand the Gates 2010</p> <p>13 paper has data on additional years of follow-up,</p> <p>14 correct?</p> <p>15 A. And additional patients.</p> <p>16 MS. O'DELL: Objection to form.</p> <p>17 Q. (BY MR. JAMES) And you understand that</p> <p>18 the Gates 2010 paper includes an analysis of the</p> <p>19 odds ratios associated with talc and ovarian cancer,</p> <p>20 correct?</p> <p>21 A. Correct.</p> <p>22 Q. Do you believe the Penninkilampi study</p> <p>23 should have included the data from the Gates 2010</p> <p>24 paper?</p>

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<p>1 A. I --</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 A. I believe it doesn't matter.</p> <p>4 Q. (BY MR. JAMES) Why doesn't it matter?</p> <p>5 A. Because we have the Berge study that did</p> <p>6 include it, and that -- for some reason, it's not</p> <p>7 included in my report, and if you don't call it a</p> <p>8 flaw, I will. I -- I think in multiple drafts and</p> <p>9 cut and pasting it went to the great cyber void.</p> <p>10 Q. Okay. And that's -- the discussion that</p> <p>11 you just had was concerning the Berge paper,</p> <p>12 correct?</p> <p>13 A. Right.</p> <p>14 Q. But returning back to the Penninkilampi</p> <p>15 study, do you believe it was a flaw for the authors</p> <p>16 not to include data from Gates 2010?</p> <p>17 MS. O'DELL: Objection to form.</p> <p>18 A. No, I don't.</p> <p>19 Q. (BY MR. JAMES) Why is that?</p> <p>20 A. Because it doesn't make any difference.</p> <p>21 Because Berge did, and it didn't make any difference</p> <p>22 in the results.</p> <p>23 Q. Okay. So I'm asking about the</p> <p>24 Penninkilampi study. And my question is whether</p>	<p>1 Q. -- "While the results of case-control</p> <p>2 studies are prone to recall bias, especially with</p> <p>3 intense media attention following the commencement</p> <p>4 of litigation in 2014, the confirmation of an</p> <p>5 association in cohort studies between perineal talc</p> <p>6 use and serous invasive ovarian cancer is suggestive</p> <p>7 of a causal association," closed quote.</p> <p>8 Do you see that?</p> <p>9 A. Yes.</p> <p>10 Q. And so Penninkilampi is hinging its</p> <p>11 conclusions on what it believes to be the results</p> <p>12 of, quote, "cohort studies," closed quote, correct?</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 A. I don't believe that they hinge their</p> <p>15 whole findings on cohort studies. Their statistical</p> <p>16 and significant include- -- significance included</p> <p>17 those cohort studies, but it's only a component of</p> <p>18 theirs.</p> <p>19 Q. (BY MR. JAMES) And certainly in the</p> <p>20 Conclusions section, the Penninkilampi authors</p> <p>21 acknowledge the bias limitations associated with</p> <p>22 case control studies, correct?</p> <p>23 A. They say case control studies are prone to</p> <p>24 recall bias. I think a better choice of words would</p>
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<p>1 Penninkilampi should have included the data from the</p> <p>2 Gates 2010.</p> <p>3 MS. O'DELL: Object to the form.</p> <p>4 A. Well, if you use the most recent available</p> <p>5 data, maybe he should have, yes, you're right.</p> <p>6 Q. (BY MR. JAMES) And, in fact, that's one</p> <p>7 of the points that you make in your report, correct?</p> <p>8 You -- one of the things you note in</p> <p>9 your report is follow-up is a good thing, right?</p> <p>10 A. Correct.</p> <p>11 Q. And the Penninkilampi authors make certain</p> <p>12 conclusions about the cohort data, don't they?</p> <p>13 A. You're gonna have to tell me what those</p> <p>14 conclusions are before I'll agree with or not agree</p> <p>15 with that.</p> <p>16 Q. Okay. Dr. Smith, if you -- do you have</p> <p>17 the Penninkilampi paper in front of you?</p> <p>18 A. I do.</p> <p>19 Q. Okay. And you see on page 47 in the</p> <p>20 Conclusions section --</p> <p>21 A. Um-hum.</p> <p>22 Q. -- you see that, quote -- and this is the</p> <p>23 second sentence down --</p> <p>24 A. Um-hum.</p>	<p>1 be may be prone to recall bias.</p> <p>2 But, yes, cohort studies obviate</p> <p>3 recall bias. They don't have it.</p> <p>4 Q. And we know again here that Penninkilampi</p> <p>5 did not include the Nurses' Health cohort data from</p> <p>6 2010 Gates, correct?</p> <p>7 MS. O'DELL: Object to the form.</p> <p>8 A. Correct.</p> <p>9 Q. (BY MR. JAMES) Okay. And are -- do you</p> <p>10 know that in the Gates 2010 paper the reported</p> <p>11 association with the serous ovarian cancer washed</p> <p>12 out?</p> <p>13 A. I know that.</p> <p>14 MS. O'DELL: Object to the form.</p> <p>15 Q. (BY MR. JAMES) And Penninkilampi</p> <p>16 apparently doesn't know that, correct?</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 A. I haven't talked to him.</p> <p>19 Q. (BY MR. JAMES) Okay. Well, Penninkilampi</p> <p>20 is referring to a confirmation of an association and</p> <p>21 cohort studies.</p> <p>22 Do you see that?</p> <p>23 A. Right.</p> <p>24 Q. So he must be referring to --</p>

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<p style="text-align: right;">Page 222</p> <p>1 A. The Gertig study.</p> <p>2 Q. -- Gertig study, correct?</p> <p>3 MS. O'DELL: Excuse me.</p> <p>4 A. Right.</p> <p>5 MS. O'DELL: Object to the form.</p> <p>6 Hey, Doctor, give me just a minute</p> <p>7 to --</p> <p>8 THE WITNESS: Okay. I'm sorry.</p> <p>9 MS. O'DELL: -- get my objection in.</p> <p>10 Q. (BY MR. JAMES) And we know that's true</p> <p>11 because we know none of the cohorts performed today</p> <p>12 have found an association, correct?</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 A. That is true.</p> <p>15 Q. (BY MR. JAMES) We know the Women's Health</p> <p>16 Initiative study did not find an association between</p> <p>17 perineal talc use and ovarian cancer, correct?</p> <p>18 MS. O'DELL: Object to the form.</p> <p>19 A. That is true.</p> <p>20 Q. (BY MR. JAMES) We know the Gonzalez</p> <p>21 Sister Study -- the prospective Gonzalez Sister</p> <p>22 Study did not find an association between perineal</p> <p>23 talc use and ovarian cancer, correct?</p> <p>24 A. That is true.</p>	<p style="text-align: right;">Page 224</p> <p>1 Q. (BY MR. JAMES) If you had looked at</p> <p>2 the Gates --</p> <p>3 MS. O'DELL: Hey, let -- finish -- if</p> <p>4 you've got an answer --</p> <p>5 Did you finish your answer?</p> <p>6 THE WITNESS: I did finish my answer.</p> <p>7 MS. O'DELL: Okay. Give me a moment.</p> <p>8 Thank you.</p> <p>9 THE WITNESS: I know. I'm not</p> <p>10 supposed to talk so fast.</p> <p>11 Q. (BY MR. JAMES) If you had looked at the</p> <p>12 Gates 2010 data, he wouldn't have been able to make</p> <p>13 that statement, correct?</p> <p>14 MS. O'DELL: Object to the form.</p> <p>15 A. Do you mean the statement that the</p> <p>16 confirmation of an association in cohort studies</p> <p>17 between perineal talc use and serous invasive cancer</p> <p>18 is suggested of a causal association?</p> <p>19 Well, his -- the Gates study did not</p> <p>20 have statistically significant increase incidence of</p> <p>21 serous ovarian cancer.</p> <p>22 Q. (BY MR. JAMES) Another reason that you'd</p> <p>23 want to look at the most recent data available from</p> <p>24 a cohort is because of concerns about latency, which</p>
<p style="text-align: right;">Page 223</p> <p>1 Q. So we can deduce here that the only study</p> <p>2 that he can be referring to is the Gertig 2000</p> <p>3 study, correct?</p> <p>4 A. He lists Gertig in his reference -- in</p> <p>5 his -- see. He lists Gertig --</p> <p>6 Q. So there's no dispute --</p> <p>7 A. -- right there.</p> <p>8 Q. I'm sorry, Doctor.</p> <p>9 A. In Gertig, there's no dispute. He's</p> <p>10 not trying to hide anything. It's listed,</p> <p>11 "Gertig 2000."</p> <p>12 Q. Right. So there's no dispute in our</p> <p>13 discussion here either that what he's referring to</p> <p>14 there is the Gertig 2000 study, correct?</p> <p>15 MS. O'DELL: Object to the form.</p> <p>16 A. He is referring to the Gertig.</p> <p>17 Q. (BY MR. JAMES) And he just forgot to look</p> <p>18 at the Gates 2010 data, correct?</p> <p>19 A. I don't know why --</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A. -- he didn't look at the Gates study.</p> <p>22 MS. O'DELL: Excuse me, Doctor.</p> <p>23 Object to the form.</p> <p>24 You may answer.</p>	<p style="text-align: right;">Page 225</p> <p>1 you also cite in your report, correct?</p> <p>2 MS. O'DELL: Objection to form.</p> <p>3 A. That's not the only reason to just look at</p> <p>4 most up-to-date studies.</p> <p>5 Q. (BY MR. JAMES) Is it one of the reasons?</p> <p>6 MS. O'DELL: Object to the form.</p> <p>7 A. I have never con- -- thought about latency</p> <p>8 in terms of looking at the most recent study and the</p> <p>9 most up-to-date studies.</p> <p>10 Q. (BY MR. JAMES) Okay. In your report, do</p> <p>11 you recall critiquing the cohort studies on the</p> <p>12 basis that, in your opinion, they have short</p> <p>13 follow-up and don't account for latency?</p> <p>14 Do you recall that critique?</p> <p>15 A. Particularly -- particularly the Gonzalez</p> <p>16 study, yes.</p> <p>17 Q. Okay. But the -- the question that I'm</p> <p>18 posing here is more general in nature.</p> <p>19 Is that one of the reasons that you</p> <p>20 would want to include the most recent data from a</p> <p>21 cohort is to, in part, address the concern of</p> <p>22 latency that you --</p> <p>23 A. The longest follow-up possible.</p> <p>24 Q. Okay. We will turn to the Berge study,</p>

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<p>1 which you previewed for us, Dr. Smith, and I will</p> <p>2 hand you a copy, if I haven't already.</p> <p>3 MR. JAMES: I'm gonna mark Berge,</p> <p>4 B-e-r-g-e, as Exhibit 24.</p> <p>5 (Deposition Exhibit 24 marked for</p> <p>6 identification.)</p> <p>7 Q. (BY MR. JAMES) Dr. Smith, I've handed you</p> <p>8 the Berge paper.</p> <p>9 And this is a paper you have seen</p> <p>10 before, correct?</p> <p>11 A. It is.</p> <p>12 Q. And as you just discussed, you acknowledge</p> <p>13 it's not discussed in your report, correct?</p> <p>14 MS. O'DELL: Objection to form.</p> <p>15 Q. (BY MR. JAMES) Or I'll -- I'm going to</p> <p>16 rephrase. I know -- I --</p> <p>17 A. I have cited it --</p> <p>18 Q. -- I can correct that.</p> <p>19 You cited it for a publication bias</p> <p>20 point, correct?</p> <p>21 A. I don't -- I'd have to look where I cited</p> <p>22 it.</p> <p>23 Q. Okay.</p> <p>24 A. I -- it's missing from here. Yeah.</p>	<p>1 A. I was looking for something, but go ahead</p> <p>2 and talk.</p> <p>3 MS. O'DELL: Excuse me. I think --</p> <p>4 let me get -- I think maybe -- do you have part of</p> <p>5 the table missing from your version?</p> <p>6 THE WITNESS: There's -- yeah, there's</p> <p>7 a table that I'm used to around here.</p> <p>8 MR. JAMES: Do you have a better copy,</p> <p>9 Leigh?</p> <p>10 THE WITNESS: Let me see.</p> <p>11 MS. O'DELL: Is it an eTable?</p> <p>12 THE WITNESS: No, I think it's just</p> <p>13 the copy . . .</p> <p>14 MR. JAMES: That's all I have.</p> <p>15 THE WITNESS: Oh, yeah. No. I don't</p> <p>16 know. Yeah, this is my copy.</p> <p>17 MR. JAMES: Okay. Let me see.</p> <p>18 And Mr. Klatt has handed me some</p> <p>19 better copies as well, if anybody needs a better one</p> <p>20 as well.</p> <p>21 MS. O'DELL: Thank you.</p> <p>22 MR. JAMES: And at the break, I will</p> <p>23 resticker.</p> <p>24 THE WITNESS: Yeah, it's Table 2 on --</p>
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<p>1 Q. Do you agree that you haven't discussed</p> <p>2 the Berge study in-depth in your report?</p> <p>3 A. Correct.</p> <p>4 Q. And that was a -- what you were alluding</p> <p>5 to earlier as a mistake and omission. Fair?</p> <p>6 MS. O'DELL: Objection to form.</p> <p>7 A. Correct.</p> <p>8 Q. (BY MR. JAMES) What are your thoughts on</p> <p>9 the Berge study?</p> <p>10 A. Again, it -- it -- it uses Gates instead</p> <p>11 of Gertig. It has very similar findings to</p> <p>12 Penninkilampi. If you look at his forest plot, he</p> <p>13 looks at the cohort studies: Gates, Houghton,</p> <p>14 Gonzalez, nurses, women, sisters. Again, they are</p> <p>15 not statistically significant on their relative risk</p> <p>16 and confidence intervals.</p> <p>17 And yet in inclusion with the entire</p> <p>18 population, his numbers are very similar to</p> <p>19 Penninkilampi with an overall relative risk slightly</p> <p>20 lower of 1.22 versus Penninkilampi is 1.31;</p> <p>21 confidence intervals 1.13 to 1.30 for Berg remains</p> <p>22 statistically significant as Penninkilampi 1.24 to</p> <p>23 1.39.</p> <p>24 Q. Do you -- Doctor, are you finished?</p>	<p>1 here it is.</p> <p>2 A. Table 2 on page 6 where Penninkilampi -- I</p> <p>3 am becoming buried -- found invasive serous.</p> <p>4 So first, I'm gonna give you</p> <p>5 Penninkilampi's statistically significant increase</p> <p>6 rate invasive serous cancer with genital talc use.</p> <p>7 Penninkilampi's numbers are overall risk 1.25,</p> <p>8 confidence interval 1.01 to 1.55.</p> <p>9 Berg -- Berge is 1.24, confident</p> <p>10 intervals 1.15 to 1.34.</p> <p>11 So this is why I told you from</p> <p>12 comparing these two papers that Gertig versus Gates,</p> <p>13 when you look at all the same body, it's six of one</p> <p>14 half-a-dozen of the other, the inclusion of which of</p> <p>15 those two post -- his studies in meta-analyses.</p> <p>16 Q. (BY MR. JAMES) But you have already</p> <p>17 agreed with me that it would have been better for</p> <p>18 Penninkilampi to included the Gates 2010 data,</p> <p>19 correct?</p> <p>20 MS. O'DELL: Objection to form.</p> <p>21 A. I like using the most recent study.</p> <p>22 Q. (BY MR. JAMES) And that's EPI 101, isn't</p> <p>23 it?</p> <p>24 MS. O'DELL: Objection; form.</p>

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<p>1 A. That's everything 101.</p> <p>2 Q. (BY MR. JAMES) And we see here in the</p> <p>3 Berge paper if we look at the conclusions in the</p> <p>4 abstract, the very last sentence of the paper, the</p> <p>5 authors conclude, quote -- and I'm at the very first</p> <p>6 page of the paper in the abstract -- they conclude,</p> <p>7 quote, "The heterogeneity of results by study</p> <p>8 design . . . however, detracts from a causal</p> <p>9 interpretation of the association."</p> <p>10 A. I think I'm in the wrong place.</p> <p>11 MS. O'DELL: What page are you on?</p> <p>12 MR. JAMES: The abstract.</p> <p>13 A. The heterogeneity.</p> <p>14 Q. (BY MR. JAMES) Dr. Smith, I think your</p> <p>15 scarf is covering your mike.</p> <p>16 A. I'm sorry. Nope. I broke it.</p> <p>17 THE VIDEOGRAPHER: Okay. We need to</p> <p>18 go off the record.</p> <p>19 MR. JAMES: Okay. Off the record.</p> <p>20 THE VIDEOGRAPHER: Okay. Off the</p> <p>21 record. The time is 3:41 p.m.</p> <p>22 (A recess was taken from 3:41 p.m.</p> <p>23 to 4:13 p.m.)</p> <p>24 THE VIDEOGRAPHER: Back on the record.</p>	<p>1 it does differ from this individual one paper.</p> <p>2 Q. (BY MR. JAMES) And, again, the individual</p> <p>3 one paper you're here is a meta-analysis that -- it</p> <p>4 is a meta-analysis, correct?</p> <p>5 A. Yes. I have -- I have great respect for</p> <p>6 this paper.</p> <p>7 Q. And we see the -- in the conclusion that</p> <p>8 we just read, one of the points the authors here</p> <p>9 make concerns the heterogeneity results by study</p> <p>10 design, correct?</p> <p>11 A. Correct.</p> <p>12 Q. And there the authors are noting that the</p> <p>13 association that appears in a subset of the case</p> <p>14 control studies is not being replicated in the</p> <p>15 cohorts prospective studies, correct?</p> <p>16 MS. O'DELL: Object to the form.</p> <p>17 A. Case control studies are entirely</p> <p>18 different from cohort studies.</p> <p>19 Q. (BY MR. JAMES) All right. Let me ask my</p> <p>20 question again.</p> <p>21 A. Okay.</p> <p>22 Q. Here when the authors are referring to the</p> <p>23 difference in the results of the types of studies,</p> <p>24 right, in this conclusion, that's what they're</p>
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<p>1 The time is 4:13 p.m.</p> <p>2 Q. (BY MR. JAMES) And, Dr. Smith, when we</p> <p>3 broke, we were discussing the Berge study, correct?</p> <p>4 A. Yes.</p> <p>5 Q. And so I'm gonna -- I think that when we</p> <p>6 broke I was pointing you toward the abstract portion</p> <p>7 of the patient -- paper.</p> <p>8 A. Correct.</p> <p>9 Q. Okay. And do you see there at the bottom</p> <p>10 of the abstract the authors there conclude, quote,</p> <p>11 "The heterogeneity of results by study design and</p> <p>12 the lack of a trend for duration and frequency of</p> <p>13 use, however, detract from a causal interpretation</p> <p>14 of this association," close quotes?</p> <p>15 A. That --</p> <p>16 MS. O'DELL: Object to form.</p> <p>17 A. That was their assessment.</p> <p>18 Q. (BY MR. JAMES) Okay. And your litigation</p> <p>19 opinion differs from the causal conclusions reached</p> <p>20 by these authors, correct?</p> <p>21 MS. O'DELL: Object to the form.</p> <p>22 A. My causal interpretation is built on the</p> <p>23 totality of all of these studies and the</p> <p>24 biochemistry and all the literature I reviewed. So</p>	<p>1 referring to, aren't they, when they say</p> <p>2 "heterogeneity"?</p> <p>3 A. I can't -- I can't define their</p> <p>4 heterogeneity.</p> <p>5 Q. Let me try again. So here the authors</p> <p>6 refer to the -- quote, "The heterogeneity of results</p> <p>7 by study design," close quote.</p> <p>8 Does that phrase -- do you understand</p> <p>9 what they mean by that phrase?</p> <p>10 A. Do they define it further in the text? I</p> <p>11 don't remember that.</p> <p>12 Q. Let's look to page 253 of the article.</p> <p>13 A. Mine has single-digit page numbers.</p> <p>14 Q. Hum.</p> <p>15 A. Starts on page 1 and goes to page 9 --</p> <p>16 oop. Because mine's an e-Pub. This is an e-Pub.</p> <p>17 MS. O'DELL: This is the copy I think</p> <p>18 you gave.</p> <p>19 MR. JAMES: Can I see that real quick?</p> <p>20 MS. O'DELL: Yeah.</p> <p>21 MR. JAMES: Is that an e-Pub as well,</p> <p>22 Leigh, on the front?</p> <p>23 BY MS. O'DELL: It --</p> <p>24 THE WITNESS: It says, "Cancer --</p>

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<p style="text-align: right;">Page 234</p> <p>1 General Cancer Position 00000."</p> <p>2 MS. O'DELL: Is that the same one</p> <p>3 you're looking at? It's just different page</p> <p>4 numbers.</p> <p>5 MR. JAMES: Um-hum.</p> <p>6 MS. O'DELL: That may be the copy</p> <p>7 that -- I think that's the copy that -- that Mike</p> <p>8 gave us.</p> <p>9 MR. JAMES: Um-hum.</p> <p>10 THE WITNESS: Because on my copy, I</p> <p>11 had to write down the final publication information</p> <p>12 beside it.</p> <p>13 MR. JAMES: Okay. I think on the next</p> <p>14 break I'm gonna take a peek closer at these Berge</p> <p>15 articles. I think we may still have a disconnect.</p> <p>16 MS. O'DELL: Okay.</p> <p>17 MR. JAMES: I'm not sure why we're</p> <p>18 looking at two different versions on the same paper.</p> <p>19 Here you go.</p> <p>20 THE WITNESS: I have written here that</p> <p>21 the final publication pages were 248 through 257 of</p> <p>22 Volume 27.</p> <p>23 Does that help you?</p> <p>24 MR. JAMES: Sort of. So let's --</p>	<p style="text-align: right;">Page 236</p> <p>1 number of studies they include.</p> <p>2 Q. (BY MR. JAMES) So as time goes on and</p> <p>3 more studies are performed testing the hypothesis of</p> <p>4 ovarian cancer in talc, that body of literature can</p> <p>5 be included in the next meta-analysis that's</p> <p>6 completed, correct?</p> <p>7 MS. O'DELL: Object to the form.</p> <p>8 A. Correct.</p> <p>9 Q. (BY MR. JAMES) You agree that the</p> <p>10 meta-analyses of all of the underlying studies</p> <p>11 cannot eliminate the recall bias in the underlying</p> <p>12 studies?</p> <p>13 MS. O'DELL: Object to the form.</p> <p>14 A. In any case control study, there exists</p> <p>15 the possibility of any recall bias.</p> <p>16 Q. (BY MR. JAMES) And putting these studies</p> <p>17 together in a meta doesn't eliminate that, correct?</p> <p>18 MS. O'DELL: Object to the form.</p> <p>19 A. No, it does not.</p> <p>20 Q. (BY MR. JAMES) And you may recall this,</p> <p>21 but the Penninkilampi study concedes that point,</p> <p>22 correct?</p> <p>23 MS. O'DELL: Object -- object to the</p> <p>24 form.</p>
<p style="text-align: right;">Page 235</p> <p>1 let's just keep moving. Okay?</p> <p>2 THE WITNESS: Okay.</p> <p>3 MR. JAMES: Let's keep plowing.</p> <p>4 Q. (BY MR. JAMES) The Berge authors made a</p> <p>5 conclusion that the evidence was insufficient to</p> <p>6 support causation, correct?</p> <p>7 MS. O'DELL: Object to the form.</p> <p>8 A. They say it detracts from causal</p> <p>9 interpretation of this association.</p> <p>10 Q. (BY MR. JAMES) And one of the items they</p> <p>11 consider is the fact that the cohort data does not</p> <p>12 report a statistically significant association</p> <p>13 between ovarian cancer and talc use, correct?</p> <p>14 A. Because they use Gates.</p> <p>15 Q. Understood.</p> <p>16 Would you agree that all of the</p> <p>17 meta-analyses that we have looked at today and that</p> <p>18 you addressed in your report are relying on a -- on</p> <p>19 a similar set of data?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A. I will certainly tell you the past three</p> <p>22 studies -- two to three studies we've looked at work</p> <p>23 on a similar data. This is a growing body of</p> <p>24 epidemiologic evidence, so each study grows in the</p>	<p style="text-align: right;">Page 237</p> <p>1 A. (No response.)</p> <p>2 Q. (BY MR. JAMES) And Dr. Smith, referring</p> <p>3 to page 47, the Conclusions section of the paper.</p> <p>4 A. Yes.</p> <p>5 Q. And we see here that the -- if you look</p> <p>6 down to --</p> <p>7 A. Yes.</p> <p>8 Q. -- the last sentence in that column, they</p> <p>9 say, "Additional epi evidence from prospective</p> <p>10 studies with attention to effects of ovarian cancer</p> <p>11 subtype is warranted."</p> <p>12 Do you see that?</p> <p>13 A. I see that.</p> <p>14 Q. And so the authors here in the</p> <p>15 Penninkilampi study are expressing a need for</p> <p>16 additional prospective data, correct?</p> <p>17 MS. O'DELL: Objection.</p> <p>18 A. Correct.</p> <p>19 Q. (BY MR. JAMES) We've talked already, in</p> <p>20 some fashion, about the cohort studies.</p> <p>21 You agree with me that the litigation</p> <p>22 opinions you're offering in your report conflict</p> <p>23 with the cohort studies, correct?</p> <p>24 MS. O'DELL: Object to the form.</p>

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<p>1 A. The cohort studies, with the exception of</p> <p>2 Gertig and serous, showed no statistically</p> <p>3 significant increase hazard ratio or relative risk</p> <p>4 or standardized mortality ratio, depending on the</p> <p>5 statistics they chose, hazard ratios for ovarian</p> <p>6 cancer. That is a fact.</p> <p>7 Q. (BY MR. JAMES) You discuss the Houghton</p> <p>8 study, the Women's Health Initiative study on</p> <p>9 page 15 of your report.</p> <p>10 A. Yes.</p> <p>11 Q. And you include the note that -- on</p> <p>12 page 15, that "No histologic information was</p> <p>13 obtained."</p> <p>14 Do you see that phrase in your report?</p> <p>15 A. I do.</p> <p>16 Q. Do you believe that to be correct?</p> <p>17 A. May I see the paper.</p> <p>18 Q. Yes, Doctor.</p> <p>19 MR. JAMES: I'm gonna mark the Women's</p> <p>20 Health Initiative Houghton study as Exhibit</p> <p>21 Number 25.</p> <p>22 (Deposition Exhibit 25 marked for</p> <p>23 identification.)</p> <p>24 THE WITNESS: Thank you.</p>	<p>1 A. They did not find any variation of risk by</p> <p>2 subtype.</p> <p>3 Q. Okay. So would you agree with me, then,</p> <p>4 that that statement in your report is erroneous?</p> <p>5 A. I believe --</p> <p>6 MS. O'DELL: Object to the form.</p> <p>7 A. I believe I -- it would have been better</p> <p>8 stated "No difference in risks by histologic</p> <p>9 information was demonstrated."</p> <p>10 Q. (BY MR. JAMES) Okay.</p> <p>11 A. What it stated here is wrong.</p> <p>12 Q. Are your opinions that you're offering</p> <p>13 today on general causation between talc and ovarian</p> <p>14 cancer histologic specific?</p> <p>15 A. With regards to mucinous ovarian cancer, I</p> <p>16 have seen no -- strike that.</p> <p>17 I learned how to say that.</p> <p>18 Q. That's fine.</p> <p>19 A. With a totality of the information I've</p> <p>20 looked at, I do not believe talcum powder is a risk</p> <p>21 factor for the development of mucinous ovarian</p> <p>22 cancer.</p> <p>23 Q. Do you believe it is a risk factor for the</p> <p>24 other subtypes of epithelial ovarian cancer?</p>
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<p>1 Q. (BY MR. JAMES) If we look at the study on</p> <p>2 page 3, Dr. Smith.</p> <p>3 A. (Examined exhibit.) Yes. Table 1?</p> <p>4 Q. You're ahead of -- you're ahead of me.</p> <p>5 MS. O'DELL: Please wait for the</p> <p>6 question, Dr. Smith.</p> <p>7 THE WITNESS: He said, "If we look at</p> <p>8 the study on page 3." That was a question.</p> <p>9 Q. (BY MR. JAMES) Yes. Yes. Yes, page 3.</p> <p>10 Page 3. I'm getting there.</p> <p>11 (Examined exhibit.) And the study</p> <p>12 states that "Associations by ovarian cancer</p> <p>13 histological subtype were evaluated."</p> <p>14 A. I'm sorry. Where are you on page 3?</p> <p>15 Q. Give me one second. I lost it. I'm on</p> <p>16 the wrong page here. Give me one second.</p> <p>17 Dr. Smith, if we turn to page 5</p> <p>18 of 6 --</p> <p>19 A. Um-hum.</p> <p>20 Q. -- we see here that there is information</p> <p>21 in the Table 4 pertaining to Histology, correct?</p> <p>22 A. I see that.</p> <p>23 Q. Okay. And do you know if this study found</p> <p>24 any variation in risk by subtype?</p>	<p>1 A. I am certain that it's a risk factor for</p> <p>2 the risk factor of serous invasive ovarian and</p> <p>3 endometrioid invasive --</p> <p>4 Did I say endometrial?</p> <p>5 Q. You did.</p> <p>6 A. Oh, I meant -- okay. Let me start again.</p> <p>7 I believe it is. It -- talcum powder</p> <p>8 products cause invasive serous ovarian cancer and</p> <p>9 invasive endometrioid ovarian cancer.</p> <p>10 I am less clear on its relation to</p> <p>11 clear cell carcinoma, and I believe it is not a</p> <p>12 causative agent in the development of mucinous</p> <p>13 ovarian cancer.</p> <p>14 Q. And when you say you're less clear with</p> <p>15 respect to clear cell, sitting here today, do you</p> <p>16 offer the opinion that talc is causative of clear</p> <p>17 cell ovarian cancer?</p> <p>18 A. It is -- yes, I will say that. Because of</p> <p>19 the inflammation, yes, I can say that.</p> <p>20 Q. So you're -- you say that you're less</p> <p>21 clear about it, but you still feel --</p> <p>22 A. I think there's less dat- --</p> <p>23 MS. O'DELL: Let him finish his</p> <p>24 question.</p>

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<p>1 Q. (BY MR. JAMES) So you --</p> <p>2 THE WITNESS: Let him finish his</p> <p>3 question.</p> <p>4 Q. (BY MR. JAMES) So you say that you're</p> <p>5 less clear about clear cell, but you were still</p> <p>6 comfortable stating that the evidence is sufficient</p> <p>7 to conclude that talc causes clear cell carcinoma?</p> <p>8 MS. O'DELL: Objection; form.</p> <p>9 A. I can say it better. Clear cell carcinoma</p> <p>10 is a less frequent histologic type, but inflammation</p> <p>11 still contributes heavily to its development. I</p> <p>12 think we have fewer cases; therefore, fewer data,</p> <p>13 but I think talc contributes to its development.</p> <p>14 Q. (BY MR. JAMES) And when you say</p> <p>15 "contributes to its development" --</p> <p>16 A. Causes.</p> <p>17 Q. -- I think you --</p> <p>18 A. In a legal term.</p> <p>19 Q. -- are you asking -- are you saying that</p> <p>20 it causes?</p> <p>21 A. Causes.</p> <p>22 Q. So your opinion here today is that talc is</p> <p>23 causative of serous?</p> <p>24 A. Serous.</p>	<p>1 MS. O'DELL: Object to the form; lack</p> <p>2 of foundation.</p> <p>3 A. I'd love to discuss it with them.</p> <p>4 Q. (BY MR. JAMES) Do you have any quarrels</p> <p>5 with the analysis on the Houghton paper?</p> <p>6 A. Could you be more specific?</p> <p>7 Q. Do you have any critiques, just sitting</p> <p>8 here today, of the Houghton paper?</p> <p>9 MS. O'DELL: Object to the form;</p> <p>10 vague.</p> <p>11 A. Well, in evaluating it, I looked at</p> <p>12 that it was small and -- well, it's 61,000</p> <p>13 postmenopausal women. It had a relatively short</p> <p>14 follow-up of only 12.4 years. The number of cases</p> <p>15 is low, about 429, so -- I mean, it's a small, short</p> <p>16 study.</p> <p>17 Q. (BY MR. JAMES) (Short pause.)</p> <p>18 And do you understand that the Women's</p> <p>19 Health Initiative included a question on duration?</p> <p>20 A. Yes.</p> <p>21 Q. Okay. Did you factor that into</p> <p>22 considering your comment on follow-up?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A. The follow-up's still 12.4 years. It</p>
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<p>1 Q. Serous endometrioid --</p> <p>2 A. Yes.</p> <p>3 Q. -- and clear cell; is that correct?</p> <p>4 A. Yes.</p> <p>5 Q. Do you consider those three subtypes of</p> <p>6 ovarian cancer to be separate diseases?</p> <p>7 MS. O'DELL: Object to the form.</p> <p>8 A. If they're -- if they're poorly</p> <p>9 differentiated, they are in the same type 2 ovarian</p> <p>10 cancer that we talk about aggressive, metastasized</p> <p>11 widely, fatal, yes.</p> <p>12 Q. (BY MR. JAMES) Do you believe that the</p> <p>13 risk factor profiles for serous, endometrioid, and</p> <p>14 clear cell are different or the same?</p> <p>15 MS. O'DELL: Object to the form.</p> <p>16 A. They're certainly overlapping.</p> <p>17 Endometriosis is generally associated more with</p> <p>18 endometrioid and clear cell carcinomas, less so with</p> <p>19 serous carcinomas.</p> <p>20 Q. (BY MR. JAMES) If other experts have</p> <p>21 reached the conclusion that the association between</p> <p>22 talc and ovarian cancer is causative -- proven</p> <p>23 causative by the science only with serous and talc,</p> <p>24 then you would disagree with those experts?</p>	<p>1 doesn't change it.</p> <p>2 Q. (BY MR. JAMES) Does the fact that they</p> <p>3 asked about duration factor into your analysis at</p> <p>4 all?</p> <p>5 A. It's better to ask about duration, but --</p> <p>6 Q. And -- I'm sorry.</p> <p>7 A. -- but it doesn't change how long the</p> <p>8 study went on with the small numbers.</p> <p>9 Q. And so the study, if -- by asking about</p> <p>10 duration is increasing data on the -- on the time</p> <p>11 period for which it's evaluating talc users,</p> <p>12 correct?</p> <p>13 A. Correct.</p> <p>14 MS. O'DELL: So off the mark. I</p> <p>15 object to that question.</p> <p>16 Q. (BY MR. JAMES) On page 16 of your report,</p> <p>17 you state that, quote, "In my opinion, meta-analyses</p> <p>18 is the most valid and reliable way to study an issue</p> <p>19 like ovarian cancer," closed quote.</p> <p>20 Did you see where I read that?</p> <p>21 A. I see "In my opinion meta-analyses</p> <p>22 provides most reliable evidence in this situation."</p> <p>23 Is there another place? That's the</p> <p>24 third -- second full paragraph.</p>

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<p style="text-align: right;">Page 246</p> <p>1 I heard you say "valid," and I</p> <p>2 don't -- I'm not seeing that word.</p> <p>3 MS. O'DELL: I think you need to look</p> <p>4 a bit further down the page.</p> <p>5 THE WITNESS: Sorry.</p> <p>6 MR. JAMES: Yeah.</p> <p>7 Q. (BY MR. JAMES) It's the next paragraph.</p> <p>8 Do you see that? It's the</p> <p>9 lead sentence --</p> <p>10 A. Yeah, okay. I'm -- okay. I'm with you</p> <p>11 now.</p> <p>12 Q. Okay. Is that statement confined to talc</p> <p>13 or to ovarian cancer in general?</p> <p>14 MS. O'DELL: Object to the form.</p> <p>15 A. No. I mean, if we're looking at treatment</p> <p>16 studies, we have the opportunity to do prospective</p> <p>17 randomized controls trials, like the Armstrong trial</p> <p>18 that's cited in here. Those are always the best</p> <p>19 forms we have for treatment. We just can't do it</p> <p>20 for exposure.</p> <p>21 Q. (BY MR. JAMES) Here you say that you</p> <p>22 consider meta-analyses to be the most valid and</p> <p>23 reliable way to study an issue like ovarian cancer,</p> <p>24 correct?</p>	<p style="text-align: right;">Page 248</p> <p>1 MS. O'DELL: Excuse me. Let me object</p> <p>2 to form of that question and the question before.</p> <p>3 MR. JAMES: A retrospective objection.</p> <p>4 MS. O'DELL: Yes, that's right.</p> <p>5 A. Prospective what type studies, please?</p> <p>6 Q. (BY MR. JAMES) Okay.</p> <p>7 A. Cohort versus randomized? Double-blind?</p> <p>8 Q. So the meta-analyses, for example, that</p> <p>9 you have described as the most valid and reliable</p> <p>10 way to study the issue have commented in the studies</p> <p>11 themselves that prospective data is a higher level</p> <p>12 of evidence.</p> <p>13 Did you know that?</p> <p>14 A. Are you talking about cohort studies that</p> <p>15 are prospective?</p> <p>16 Q. Correct, prospective cohort studies.</p> <p>17 A. Okay.</p> <p>18 MS. O'DELL: Object to the form.</p> <p>19 A. Which can be analyzed by meta-analysis as</p> <p>20 well.</p> <p>21 Q. (BY MR. JAMES) But the meta-analyses</p> <p>22 themselves that you have cited have discussed --</p> <p>23 A. Contain retrospective studies.</p> <p>24 Q. Excuse me. Just one second.</p>
<p style="text-align: right;">Page 247</p> <p>1 MS. O'DELL: Object to the form; asked</p> <p>2 and answered.</p> <p>3 A. I think meta-analysis is most valid and</p> <p>4 reliable way to study risk in ovarian cancer.</p> <p>5 Perhaps the word "issue" was not the best word</p> <p>6 choice.</p> <p>7 Q. (BY MR. JAMES) So you believe that</p> <p>8 meta-analysis is the best way to study risk factors</p> <p>9 for ovarian cancer?</p> <p>10 MS. O'DELL: Object to the form.</p> <p>11 A. Yes.</p> <p>12 Q. (BY MR. JAMES) Do you understand that the</p> <p>13 literature that we have discussed today, prospective</p> <p>14 cohort studies, meta-analyses, case control studies</p> <p>15 commonly make the comment about the advantages</p> <p>16 over -- excuse me -- the advantages of prospective</p> <p>17 studies over retrospective studies?</p> <p>18 A. Absolutely.</p> <p>19 Q. And those studies that make those comments</p> <p>20 are the studies that look at the issue of talc and</p> <p>21 ovarian cancer.</p> <p>22 MS. O'DELL: Excuse me. Make --</p> <p>23 Q. (BY MR. JAMES) Correct?</p> <p>24 A. Are you talking about --</p>	<p style="text-align: right;">Page 249</p> <p>1 The meta-analyses that you have cited</p> <p>2 and relied upon have discussed the fact that</p> <p>3 prospective cohort studies are higher level</p> <p>4 evidence.</p> <p>5 Did you know that?</p> <p>6 MS. O'DELL: Object to the form.</p> <p>7 A. In general, I know that.</p> <p>8 Q. (BY MR. JAMES) The cohorts themselves in</p> <p>9 their methodology sections and discussion sections</p> <p>10 talk about the fact that they are being studied</p> <p>11 prospectively for the purpose of eliminating recall</p> <p>12 bias.</p> <p>13 Do you understand that?</p> <p>14 MS. O'DELL: Object to the form.</p> <p>15 A. That is one bias that can be eliminated in</p> <p>16 a prospective cohort study, but they're both Level 4</p> <p>17 evident epidemiologic studies which comes fourth</p> <p>18 down the scale on the validity of scientific papers.</p> <p>19 Q. (BY MR. JAMES) For example, the Houghton</p> <p>20 study that we've looked at today says that "The</p> <p>21 prospective nature of our study would eliminate the</p> <p>22 potential for recall bias."</p> <p>23 Would you agree with that statement?</p> <p>24 A. Yes.</p>

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<p style="text-align: right;">Page 250</p> <p>1 Q. The Gertig study that we've discussed</p> <p>2 today says that they have prospectively examined the</p> <p>3 relationship in a large cohort of U.S. women given</p> <p>4 the concerns for recall and selection bias.</p> <p>5 Do you understand that?</p> <p>6 MS. O'DELL: Objection to form.</p> <p>7 A. I understand that.</p> <p>8 Q. (BY MR. JAMES) So these studies are</p> <p>9 performed to address the flaws in the case control</p> <p>10 studies, correct?</p> <p>11 MS. O'DELL: Object to the form.</p> <p>12 A. They are a different type of study and</p> <p>13 they do account for recall bias, but they have their</p> <p>14 own weakness and limitations.</p> <p>15 Q. (BY MR. JAMES) And we've already talked</p> <p>16 about today that, even in the Penninkilampi study</p> <p>17 that you've discussed in your report, they conclude</p> <p>18 with a note that prospective studies are warranted,</p> <p>19 correct?</p> <p>20 MS. O'DELL: Object to the form;</p> <p>21 misrepresents the document.</p> <p>22 A. They conclude with a note that prospective</p> <p>23 studies are warranted.</p> <p>24 Q. (BY MR. JAMES) If we look back at the</p>	<p style="text-align: right;">Page 252</p> <p>1 MR. JAMES: In that section.</p> <p>2 A. I have read this three times, and I'm not</p> <p>3 seeing it. Proposal: To Research Community.</p> <p>4 Q. (BY MR. JAMES) Huh.</p> <p>5 A. Are you looking at the next page, the next</p> <p>6 to the last paragraph?</p> <p>7 Q. Oh. Yes. Thank you.</p> <p>8 A. Okay.</p> <p>9 Q. Page 3.</p> <p>10 A. Page --</p> <p>11 Q. It's the second to the last paragraph.</p> <p>12 A. I gotcha. "While it would not be</p> <p>13 reasonable"?</p> <p>14 Q. Yes, Doctor.</p> <p>15 A. Okay. Yes, I see that.</p> <p>16 Q. Okay. Again, they're calling there for</p> <p>17 cohort studies, cohort prospective studies, correct?</p> <p>18 MS. O'DELL: Object to the</p> <p>19 mischaracterization.</p> <p>20 A. Correct.</p> <p>21 Q. (BY MR. JAMES) And we know that after the</p> <p>22 Langseth 2008 paper, we did have additional cohort</p> <p>23 data published, correct?</p> <p>24 A. The Gates follow-up, you mean?</p>
<p style="text-align: right;">Page 251</p> <p>1 Langseth study.</p> <p>2 MS. O'DELL: 19.</p> <p>3 Q. (BY MR. JAMES) Did you locate it before I</p> <p>4 did?</p> <p>5 A. I got it.</p> <p>6 Q. Okay. I'm coming behind you here. You</p> <p>7 see on page 3 --</p> <p>8 A. My -- it's not paginated, but I'm on the</p> <p>9 third page.</p> <p>10 Q. Oh, thank you. And it's actually -- it</p> <p>11 should be on page 2 because there's only three</p> <p>12 pages.</p> <p>13 A. Okay.</p> <p>14 MS. O'DELL: Is there a specific place</p> <p>15 you want her to read?</p> <p>16 MR. JAMES: I'm still looking.</p> <p>17 (Examined exhibit.)</p> <p>18 Q. (BY MR. JAMES) Do you see in the bottom</p> <p>19 paragraph where the authors there call for the --</p> <p>20 A. "Proposal; To Research Community?"</p> <p>21 Q. Yes. They call for the performance of</p> <p>22 prospective studies.</p> <p>23 MS. O'DELL: Is there a specific place</p> <p>24 you're pointing her to?</p>	<p style="text-align: right;">Page 253</p> <p>1 Q. We had the Gates 2010 paper, correct? The</p> <p>2 Houghton WHI 2014 paper, correct?</p> <p>3 Can you verbally answer, please?</p> <p>4 A. Yes. I'm sorry.</p> <p>5 Q. And the Gonzalez 2016 prospective paper,</p> <p>6 correct?</p> <p>7 A. Correct.</p> <p>8 Q. On page 16, you also remark that "The</p> <p>9 cohort studies were not designed specifically to</p> <p>10 look at talcum powder."</p> <p>11 Do you remember making that remark?</p> <p>12 MS. O'DELL: Where are you?</p> <p>13 MR. JAMES: On page 16 of Dr. Smith's</p> <p>14 report.</p> <p>15 BY MS. O'DELL: Oh, 16.</p> <p>16 Q. (BY MR. JAMES) It's the third par- --</p> <p>17 third full paragraph down. "In my opinion"</p> <p>18 paragraph.</p> <p>19 A. "In my opinion, meta-analysis is the most</p> <p>20 valid and reliable way to study an issue like</p> <p>21 ovarian cancer, which is relatively rare and</p> <p>22 requires a long study period to detect. The cohort</p> <p>23 studies were not designed specifically to look at</p> <p>24 talcum powder. Instead, the use of talcum powder is</p>

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<p>1 only one of many queries." 2 Q. And that's the question I'm asking you 3 right now. 4 So there you make the remark that 5 cohort studies were not designed specifically to 6 look at talc. 7 Is that a criticism you have of the 8 cohort studies? 9 MS. O'DELL: Objection to the -- 10 object to the form; misstates what's in Dr. -- 11 Go ahead, Doctor. 12 A. I don't find it particularly critical. I 13 mean, that -- they're studying lots of things. 14 Q. (BY MR. JAMES) So you do not include a 15 criticism against the cohort studies for the fact 16 that talcum powder is only one of many queries? 17 A. That is not a criticism. 18 Q. You also make the claim, and if you 19 continue on reading, Doctor, that there's a lack of 20 power in the cohort studies? 21 A. Yes. 22 Q. Okay. And what is that based on? 23 (Deposition Exhibit 26 referenced.) 24 A. The numbers. "Power" is the numbers.</p>	<p>1 A. Which table does it have on it? Does it 2 have Table 2 on it? 3 Q. Yeah. We're looking at page 6 -- 4 A. Okay. 5 Q. -- of Table 2. 6 A. Table 2 page. 7 Q. Yes. Thanks, Doctor. 8 A. All right. Now, okay, so right-hand or 9 left-hand column? 10 Q. It's the right-hand column. 11 A. Okay. Paragraph number? 12 Q. It's the first full paragraph -- 13 A. Okay, great. 14 Q. -- in the right-hand column. 15 A. Got it. 16 Q. And are you reading that paragraph? 17 A. Yes. 18 Q. Thank you. 19 A. (Examined exhibit.) He's talking about 20 heterogeneity. I don't think he's . . . 21 Q. So that -- Doctor, may I ask you a 22 question? 23 A. Certainly. 24 Q. All right.</p>
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<p>1 Steven Narod, who is a medical 2 oncologist and epidemiologist, suggests that in 3 cohort studies the critical threshold for finding -- 4 because of the rarity of ovarian cancer, the 5 critical number base is 200,000. 6 Only did one cohort study, which is 7 Gates, reach 200,000. 8 Houghton -- Houghton had 61,576 women. 9 Gonzalez had only 41,654 sisters. 10 Kind of tiny and underpowered or lack 11 of power, and those are epidemiologic terms. 12 Q. Did you consider the statements in Berge 13 about the power of the cohorts? 14 A. I'd have to look at Berge again to see 15 what that was. I found it. 16 Where do you see that? 17 Q. If you look at the right column, the first 18 full paragraph. 19 A. What page, please? 20 Q. Oh, thank you. 21 A. Oh, do you have a prob- -- 22 Q. It's page -- 23 A. Is this your bad problem? 24 Q. Yes. We're gonna --</p>	<p>1 So that paragraph concludes with the 2 statement that, quote, "Low power of cohort studies 3 cannot be invoked as explanation of the 4 heterogeneity results," closed quote, correct? 5 A. I am -- I agree with you that that is what 6 it says. 7 Q. Okay. 8 A. I cannot agree to that interpretation. 9 Q. Have you performed your own power 10 calculations in this case? 11 A. I have not. 12 Q. Okay. Do you have any reason to disagree 13 with the power calculations set forth in the Berge 14 paper? 15 MS. O'DELL: Object to the form. 16 A. The data from the Narod paper. 17 Q. (BY MR. JAMES) Do you have any other 18 basis upon which you would disagree with the Berge 19 power calculations? 20 A. No. 21 Q. On page 16 of your report, you discuss a 22 range by which you believe the risk of ovarian 23 cancer is increased by way of talc use, and you 24 conclude that it is a 20 to 50 percent range.</p>

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<p style="text-align: right;">Page 258</p> <p>1 Do you see where I am?</p> <p>2 A. I know I wrote that, but -- yes, I found</p> <p>3 it.</p> <p>4 Q. Super.</p> <p>5 It's in the paragraph --</p> <p>6 A. Right.</p> <p>7 Q. -- above Mechanisms?</p> <p>8 A. Right.</p> <p>9 Q. Where do you get that range from?</p> <p>10 A. Smith-Bindman. I don't think I -- I --</p> <p>11 okay. So over all the studies, the meta-analyses,</p> <p>12 they ran from a 1.2 to a serous subtype 1.5.</p> <p>13 In that range, it -- that would be a</p> <p>14 50 -- 20 to 50 percent increase in ovarian cancer.</p> <p>15 Q. In the course of answering that question,</p> <p>16 did you reference Smith-Bindman?</p> <p>17 A. Yeah, at the time I wrote this report, I</p> <p>18 hadn't seen her individual analysis, so I couldn't</p> <p>19 have had that information when I wrote this. I have</p> <p>20 seen it subsequently.</p> <p>21 Q. When you did look at that report?</p> <p>22 A. Her deposition. Probably, I don't know, a</p> <p>23 week-and-a-half ago, week ago. The days are running</p> <p>24 together. Maybe as much as two weeks ago. I don't</p>	<p style="text-align: right;">Page 260</p> <p>1 Dr. Plunkett?</p> <p>2 A. No.</p> <p>3 Q. Those reports that you are provided in</p> <p>4 this case were selected for you by plaintiffs'</p> <p>5 counsel, correct?</p> <p>6 MS. O'DELL: Object to the form.</p> <p>7 A. Those two reports.</p> <p>8 Q. (BY MR. JAMES) So to opine that there's a</p> <p>9 20 to 50 percent increased risk for ovarian cancer</p> <p>10 by way of talc use, you said that you -- how did you</p> <p>11 get to the 50 percent again?</p> <p>12 A. That was a high limit in serous in</p> <p>13 Gerrig --</p> <p>14 Q. In Gertig?</p> <p>15 A. -- Gertig. In Gertig.</p> <p>16 The low range was 1 point. I think</p> <p>17 it's 22 or 21. So I put that range.</p> <p>18 Q. And do you have any opinion about where</p> <p>19 the risk actually falls in that range?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A. Let's say it's 20 percent. Let's look at</p> <p>22 the lowest possible increase in risk. And let's</p> <p>23 look at the percentage of women who use talc.</p> <p>24 We -- when you use various parameters</p>
<p style="text-align: right;">Page 259</p> <p>1 remember it in relation to Christmas.</p> <p>2 MS. O'DELL: Do you remember -- do --</p> <p>3 are you referring to her report?</p> <p>4 A. Is that her report? Oh, yes, it's not her</p> <p>5 deposition. It's her report.</p> <p>6 Q. (BY MR. JAMES) Did you look at any other</p> <p>7 expert reports in this litigation that we haven't</p> <p>8 discussed today?</p> <p>9 A. I have seen Plunkett.</p> <p>10 Q. Okay. Any others?</p> <p>11 MS. O'DELL: Other than the ones we've</p> <p>12 talked about previously.</p> <p>13 A. Crowley, Longo. None of the GYN</p> <p>14 oncologists. I can't think of any other.</p> <p>15 Q. (BY MR. JAMES) Do you know why you were</p> <p>16 provided the Smith-Bindman report?</p> <p>17 A. Can I tell you why I enjoyed it?</p> <p>18 Q. No.</p> <p>19 Do you know why you were provided it?</p> <p>20 A. I suppose the lawyers wanted me to read</p> <p>21 it.</p> <p>22 Q. Did you ask for it?</p> <p>23 A. No.</p> <p>24 Q. Did you ask for the report from</p>	<p style="text-align: right;">Page 261</p> <p>1 such as Narod did, you're going to come up with</p> <p>2 hundreds of lives interrupted by ovarian cancer. So</p> <p>3 even a 20 percent increase is amazingly clinically</p> <p>4 significant and severe.</p> <p>5 Q. (BY MR. JAMES) Dr. Smith, with due</p> <p>6 respect, that wasn't the question that I asked you.</p> <p>7 A. Okay.</p> <p>8 Q. My question to you is: You've cited in</p> <p>9 your report a range of a 20 to 50 percent increased</p> <p>10 risk of ovarian cancer, correct?</p> <p>11 A. Yes.</p> <p>12 Q. And my question is: Do you have an</p> <p>13 opinion about where -- a more precise opinion about</p> <p>14 where the risk actually falls in that range?</p> <p>15 MS. O'DELL: Object -- object to</p> <p>16 the --</p> <p>17 A. I --</p> <p>18 MS. O'DELL: -- form. The report</p> <p>19 speaks for itself.</p> <p>20 A. I think that range encompassed what the</p> <p>21 truth is. I don't know an exact number that I can</p> <p>22 give you.</p> <p>23 Q. (BY MR. JAMES) And when you answered my</p> <p>24 question in discussion about the 20 percent</p>

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<p>1 increased risk . . .</p> <p>2 A. I was giving you the lowest number.</p> <p>3 Q. And you answered my question -- in the</p> <p>4 manner that you answered my question, that's with</p> <p>5 the assumption that it is a real increased risk,</p> <p>6 correct?</p> <p>7 MS. O'DELL: Object to the form.</p> <p>8 A. Correct.</p> <p>9 Q. (BY MR. JAMES) On page 16 and 17 of your</p> <p>10 report, you include a discussion of migration?</p> <p>11 A. Yes.</p> <p>12 Q. And you include the phrase that it is,</p> <p>13 quote, "universally accepted," close quote, by the</p> <p>14 gynecological community --</p> <p>15 A. Correct.</p> <p>16 Q. -- that "the female genital tract</p> <p>17 functions as a conduit for foreign material to enter</p> <p>18 the peritoneal cavity."</p> <p>19 Do you see where I was reading?</p> <p>20 A. I see exactly where it's reading.</p> <p>21 Q. On what basis do you support your claim</p> <p>22 that it is universally accepted?</p> <p>23 A. It's what we teach medical students and</p> <p>24 residents. We have the data of Egli and Sjösten</p>	<p>1 have gone from outside to inside.</p> <p>2 Q. We've talked about the IARC today,</p> <p>3 correct?</p> <p>4 A. Yes.</p> <p>5 Q. Do you know that the IARC has called the</p> <p>6 evidence concerning migration to be relatively weak?</p> <p>7 A. May I see that statement?</p> <p>8 Q. I'm asking you if you're familiar with it?</p> <p>9 A. I don't remember that statement.</p> <p>10 Q. You referenced the FDA statement on</p> <p>11 migration.</p> <p>12 What are you referring to there?</p> <p>13 A. I think they say it's something like</p> <p>14 universally accepted or everybody acknowledges. I</p> <p>15 don't remember the exact words, but they -- they say</p> <p>16 that it's what happens.</p> <p>17 Q. Do you know if the FDA statement you're</p> <p>18 referring to pertains specifically to talc?</p> <p>19 A. No, it doesn't particularly -- it --</p> <p>20 it . . .</p> <p>21 MS. O'DELL: If you need to see the</p> <p>22 statement again, Doctor --</p> <p>23 THE WITNESS: Okay. It should --</p> <p>24 BY MS. O'DELL: -- please take a look.</p>
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<p>1 and -- starts with a K -- uterine peristalsis, and</p> <p>2 the Alba tubal transport dysfunction literature</p> <p>3 through infermil- -- infertility. Looking at</p> <p>4 nonflagellated particles that go through from the</p> <p>5 outside world to the peritoneal cancer -- peritoneal</p> <p>6 cavity via the vagina, cervix, uterus, fallopian</p> <p>7 tube, peritoneal cavity.</p> <p>8 We certainly have all the</p> <p>9 bacteriologic information from chlamydia. Looking</p> <p>10 at the shot we have all the information --</p> <p>11 consistent information on decreasing incidence of</p> <p>12 ovarian cancer with tubal ligation, with</p> <p>13 hysterectomy that blocks that open channel.</p> <p>14 This is -- this is universally</p> <p>15 accepted in my gynecologic/obstetric population.</p> <p>16 I've seen it cited in the FDA without footnote.</p> <p>17 It's kind of like the sun's gonna rise tomorrow and</p> <p>18 things get from the outside world to the peritoneal</p> <p>19 cavity through the patent genital tract of a woman.</p> <p>20 Q. Do you believe it's universally accepted</p> <p>21 that talc is one of the foreign materials that can</p> <p>22 migrate through the genital tract?</p> <p>23 A. I believe it is. It's a particulate.</p> <p>24 It's in the range of all the particles that -- that</p>	<p>1 THE WITNESS: -- be on the bottom down</p> <p>2 here.</p> <p>3 You want to pull IARC while you're</p> <p>4 there?</p> <p>5 I know it's here. It's one of the</p> <p>6 early, early -- nope. We're getting there.</p> <p>7 BY MS. O'DELL: Here you go.</p> <p>8 THE WITNESS: We're getting close to</p> <p>9 it.</p> <p>10 BY MS. O'DELL: (Inaudible.)</p> <p>11 THE WITNESS: I got it. And that's --</p> <p>12 that's the petition. Here's the FDA.</p> <p>13 BY MS. O'DELL: No, no. That's --</p> <p>14 Q. (BY MR. JAMES) Here, I'll see if I can</p> <p>15 find somewhere.</p> <p>16 A. 8?</p> <p>17 Q. Did we find the FDA letter?</p> <p>18 MS. O'DELL: Exhibit 8.</p> <p>19 MR. JAMES: Okay. Super.</p> <p>20 A. (Examined exhibit.) I am not finding what</p> <p>21 I'm looking for.</p> <p>22 Q. (BY MR. JAMES) You want to look on page 5</p> <p>23 of the letter, Dr. Smith? I think that's where</p> <p>24 you're looking.</p>

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<p>1 A. Oh, okay.</p> <p>2 Q. And it's the third full paragraph down.</p> <p>3 A. Here we go. Here we go.</p> <p>4 (Examined exhibit.) Right. "The</p> <p>5 potential for particulates to migrate from the</p> <p>6 perineum and vagina to the peritoneal cavity is</p> <p>7 indisputable."</p> <p>8 Q. So that statement is not a direct</p> <p>9 statement about talc, correct?</p> <p>10 A. Correct.</p> <p>11 MS. O'DELL: Object to the form.</p> <p>12 Q. (BY MR. JAMES) You say in the section of</p> <p>13 your report that you reviewed the small number of</p> <p>14 articles that dispute talcum powder's ability to</p> <p>15 reach the tubes and ovaries, but that you, quote,</p> <p>16 "rejected those claims."</p> <p>17 Do you see that passage of your</p> <p>18 report?</p> <p>19 A. Yes.</p> <p>20 Q. What studies did you review and reject?</p> <p>21 A. The one with the cynomolgus monkeys -- I</p> <p>22 can't say that right, cynologus monkeys. I know the</p> <p>23 name of the author.</p> <p>24 Q. Are there any other studies that --</p>	<p>1 talc -- I mean, not talc -- corn starch on gloves,</p> <p>2 seeing those pelvic exam under anesthesia and then</p> <p>3 looking for starch in the peritoneum when the ladies</p> <p>4 get a subsequent hysterectomy, some of the patients</p> <p>5 did not have starch particles go through, but the</p> <p>6 majority did. So it doesn't have to go through</p> <p>7 every time to prove a point.</p> <p>8 Q. Do you believe you conducted a</p> <p>9 comprehensive review of the literature relevant to</p> <p>10 the issue of migration?</p> <p>11 A. I do.</p> <p>12 Q. Did you review all of the relevant animal</p> <p>13 studies pertaining to the issue of migration?</p> <p>14 A. I tried to. I know more about rat and</p> <p>15 rabbit ovaries than I want to.</p> <p>16 MS. O'DELL: There's no question</p> <p>17 pending, Doctor. Thank you.</p> <p>18 Q. (BY MR. JAMES) You discussed the tubal</p> <p>19 ligation data earlier --</p> <p>20 A. Yes.</p> <p>21 Q. -- correct?</p> <p>22 A. Yes.</p> <p>23 Q. Okay. What is your view on the tubal</p> <p>24 ligation data? Do you find the data there</p>
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<p>1 A. There's two of them.</p> <p>2 Q. Sorry, Doctor.</p> <p>3 A. I'm sorry. There's one with -- there's</p> <p>4 one with two monkeys, and there's one with six</p> <p>5 monkeys or five monkeys, about like that.</p> <p>6 Anyhow, they didn't -- they put</p> <p>7 particulate in the vagina. It did not transport</p> <p>8 into the peritoneal cavity of these sacrifice</p> <p>9 monkeys. And I apologize for spacing out on the</p> <p>10 name of the author. Um --</p> <p>11 Q. Are -- sorry, Doctor.</p> <p>12 MS. O'DELL: Yes, go ahead. Sorry.</p> <p>13 A. There's a rodent study by Wiener, Weiner</p> <p>14 that did not get -- well, everything went through,</p> <p>15 including the controls for black carbon and then</p> <p>16 nothing went through. Let me think of the author of</p> <p>17 those monkeys. Nothing went through in the next set</p> <p>18 of experiments.</p> <p>19 The absence of evidence is not</p> <p>20 evidence of absence. The fact that it doesn't go</p> <p>21 through in somebody's study is not as significant as</p> <p>22 it does go through in somebody else's.</p> <p>23 Q. (BY MR. JAMES) In somebody else's study?</p> <p>24 A. Right. Like even the Sjösten person with</p>	<p>1 consistent or inconsistent?</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 A. I find it consistent.</p> <p>4 MS. O'DELL: Excuse me. Sorry. Keep</p> <p>5 going.</p> <p>6 Q. (BY MR. JAMES) And earlier today, we</p> <p>7 discussed the Terry 2013 study, correct?</p> <p>8 A. Yes.</p> <p>9 Q. Okay. Do you know what the Terry study</p> <p>10 had to say about the tu- -- tubal ligation</p> <p>11 hypothesis?</p> <p>12 A. Not without looking at it. Uh-oh. I've</p> <p>13 got that bad copy that's missing part of a page.</p> <p>14 Q. That's a different copy, Doctor.</p> <p>15 A. That's Katherine Terry.</p> <p>16 Q. Oh, is it?</p> <p>17 A. The first study. It's got a badly copied</p> <p>18 page, so we had to go to the originals. I don't</p> <p>19 know if it's on that page, but . . .</p> <p>20 MS. O'DELL: I've got it here.</p> <p>21 A. Oh, here. I found the -- the tubal</p> <p>22 ligation paper -- chart is on a different page.</p> <p>23 It's not the bad page.</p> <p>24 Q. (BY MR. JAMES) And are you looking at</p>

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<p style="text-align: right;">Page 270</p> <p>1 page 819, Doctor?</p> <p>2 A. Yes.</p> <p>3 Q. Okay.</p> <p>4 A. This has in the cases with ovarian cancer</p> <p>5 there was a lower incidence of tubal ligation than</p> <p>6 in the controls in this study.</p> <p>7 Q. You'd agree the data of the Terry paper is</p> <p>8 not supportive of the tubal ligation hypothesis,</p> <p>9 correct?</p> <p>10 MS. O'DELL: Objection; form.</p> <p>11 A. In this study, the cases had a lower</p> <p>12 instance of ligation than the patients with ovarian</p> <p>13 cancer. So this is not a data point in the whole</p> <p>14 literature of tubal ligation and its protective</p> <p>15 effects.</p> <p>16 Q. (BY MR. JAMES) Did you discuss this</p> <p>17 finding of the Terry paper in your report?</p> <p>18 A. I don't think I did.</p> <p>19 Q. Why not?</p> <p>20 A. Because I think I made a -- a very broad</p> <p>21 statement about tubal ligation.</p> <p>22 Do you know exactly where that is?</p> <p>23 Q. Are we looking at the report or the paper,</p> <p>24 Doctor?</p>	<p style="text-align: right;">Page 272</p> <p>1 menopausal status."</p> <p>2 Do you see where I'm reading? I'm on</p> <p>3 page 14 of your report.</p> <p>4 A. I don't think -- I think it came out to be</p> <p>5 not statistically significant.</p> <p>6 Q. Correct.</p> <p>7 So you do have this report in here,</p> <p>8 correct?</p> <p>9 A. Yeah.</p> <p>10 Q. Okay. So the data, according to your</p> <p>11 report on tubal ligation, is inconsistent, isn't it?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A. This single study does not support my</p> <p>14 earlier station. But again, the totality of the</p> <p>15 literature on tubal ligation supports it as</p> <p>16 decreasing risk factor for ovarian carcinoma and</p> <p>17 even your -- some of the other things cited tubal</p> <p>18 ligation.</p> <p>19 MS. O'DELL: What are you looking for,</p> <p>20 Doctor?</p> <p>21 THE WITNESS: SGO and the PDQ risk</p> <p>22 factors.</p> <p>23 MS. O'DELL: Uh-huh.</p> <p>24 THE WITNESS: Yeah.</p>
<p style="text-align: right;">Page 271</p> <p>1 A. I'm looking at the report on tubal</p> <p>2 ligation.</p> <p>3 MS. O'DELL: I think you're looking</p> <p>4 for page 3, Doctor.</p> <p>5 THE WITNESS: About what?</p> <p>6 MS. O'DELL: Page 3.</p> <p>7 THE WITNESS: Back to page 3?</p> <p>8 A. Oh, the risk? There it is. "Additionally</p> <p>9 there are factors that are recognized as protective</p> <p>10 that include tubal ligation, oral contraceptive use,</p> <p>11 salpingectomy, salpingo-oophorectomy, hysterectomy,</p> <p>12 and breastfeeding."</p> <p>13 Yes, I did not cite the Terry study.</p> <p>14 Q. (BY MR. JAMES) And then on page 14 of</p> <p>15 your report is where you include a more detailed</p> <p>16 discussion of Terry, correct?</p> <p>17 A. Yes.</p> <p>18 Q. Do you include any discussion there of the</p> <p>19 tubal ligation data in that setting?</p> <p>20 A. I do not.</p> <p>21 Q. In fact, you do say here that -- just for</p> <p>22 all candor here, Doctor, if we look on page 14 of</p> <p>23 your paper, you say that "There was no association</p> <p>24 with parity, OC use, tubal ligation status, or</p>	<p style="text-align: right;">Page 273</p> <p>1 A. "If a patient has her tubes tied, a tubal</p> <p>2 ligation, her risk is deeply reduced."</p> <p>3 "Tubal ligation benefits based on</p> <p>4 solid evidence, tubal ligation is associated with a</p> <p>5 decreased risk of ovarian cancer."</p> <p>6 Q. (BY MR. JAMES) Do you find those SGO and</p> <p>7 ACOG statements that you just referred to to be</p> <p>8 informative about risk factors for ovarian cancer?</p> <p>9 MS. O'DELL: Object to the form.</p> <p>10 A. No. What I found to be informative of my</p> <p>11 assessment of tubal ligation is a comprehensive view</p> <p>12 of all the literature on tubal ligation through</p> <p>13 numerous papers and a full report that ultimately</p> <p>14 was cut out of this in one of my reports in the</p> <p>15 early drafts.</p> <p>16 MS. O'DELL: Don't discuss drafts.</p> <p>17 THE WITNESS: I'm sorry.</p> <p>18 MS. O'DELL: Thank you.</p> <p>19 THE WITNESS: I'm sorry. I dropped it</p> <p>20 again.</p> <p>21 A. I have completely reviewed the literature.</p> <p>22 I know all the literature on tubal ligation. You</p> <p>23 have -- I mentioned earlier the -- the Cramer study</p> <p>24 that shows tubal ligation increased ovarian cancer;</p>

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<p>1       whereas, Terry's not statistically significant, but</p> <p>2       that's beta error, finding difference where none</p> <p>3       exist.</p> <p>4               The -- the totality of the literature,</p> <p>5       not just a couple of funky websites, tell me that</p> <p>6       tubal ligation decreases the incidence of ovarian</p> <p>7       cancer, and that is because it interrupts the</p> <p>8       conduit from the outer world to the peritoneal</p> <p>9       cavity.</p> <p>10       Q. (BY MR. JAMES) Do you have the Terry</p> <p>11       paper in front of you still, Dr. Smith?</p> <p>12       A. Yes.</p> <p>13       Q. Okay. If we look at page 819, in the</p> <p>14       right-hand column, the bottom first --</p> <p>15               MS. O'DELL: Excuse me, Scott. Can</p> <p>16       you give me just a minute to get there? I can't</p> <p>17       find it.</p> <p>18               MR. JAMES: Sure.</p> <p>19               MS. O'DELL: Yeah. Thank you.</p> <p>20               What page?</p> <p>21               MR. JAMES: 819, the bottom first full</p> <p>22       paragraph that leads with the words, "The biological</p> <p>23       plausibility."</p> <p>24       A. Um-hum. I'm there.</p>	<p>1       oxidative stress, and elevated and inflammatory</p> <p>2       cytokines."</p> <p>3               Do you see that per- -- that sentence</p> <p>4       that I read?</p> <p>5       A. I do.</p> <p>6       Q. Okay.</p> <p>7       A. Yes.</p> <p>8       Q. Do you agree with the Terry authors that</p> <p>9       that is a hypothesis?</p> <p>10               MS. O'DELL: Objection to form.</p> <p>11       A. Yes. I think at the time this was</p> <p>12       written . . .</p> <p>13               Yes, I think that is a hypothesis that</p> <p>14       many people have drawn and is drawn in this paper.</p> <p>15       Q. (BY MR. JAMES) Dr. Smith, with respect to</p> <p>16       your report section that discusses NSAIDs. So I'm</p> <p>17       moving on.</p> <p>18       A. Yes.</p> <p>19               MS. O'DELL: Hey, Scott, if you're</p> <p>20       moving on to another topic, can we take a short</p> <p>21       break?</p> <p>22               MR. JAMES: Absolutely.</p> <p>23               MS. O'DELL: Thank you.</p> <p>24               THE VIDEOGRAPHER: Going off the</p>
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<p>1       Q. (BY MR. JAMES) Do you see where I am?</p> <p>2       A. Yes, I am.</p> <p>3       Q. Okay. If you drop down about halfway</p> <p>4       through that paragraph --</p> <p>5       A. Uh-huh.</p> <p>6       Q. -- the article states, quote,</p> <p>7       "Talc-containing powders are hypothesized to promote</p> <p>8       cancer development by ascending the female genital</p> <p>9       tract and interacting directly with the ovarian</p> <p>10       surface epithelium leading to local inflammation."</p> <p>11       A. Correct.</p> <p>12       Q. Do you agree with the Terry</p> <p>13       characterization of that?</p> <p>14               MS. O'DELL: Would you mind reading</p> <p>15       the full sentence, please?</p> <p>16       A. "Talc" --</p> <p>17               MS. O'DELL: Excuse me. Not you.</p> <p>18               THE WITNESS: Oh, sorry.</p> <p>19               MR. JAMES: Sure. Where did I leave</p> <p>20       off, Leigh?</p> <p>21               MS. O'DELL: You left off "leading to</p> <p>22       local inflammation," and then you stopped.</p> <p>23       Q. (BY MR. JAMES) Okay. "Characterized by</p> <p>24       increased rates of cell division, DNA repair,</p>	<p>1       record. The time is 5:17 p.m.</p> <p>2               (A recess was taken from 5:17 p.m.</p> <p>3               to 5:37 p.m.)</p> <p>4               THE VIDEOGRAPHER: This marks the</p> <p>5       beginning of Disk 3 -- excuse me, Disk 4. Back on</p> <p>6       the record. The time is 5:37 p.m.</p> <p>7       Q. (BY MR. JAMES) Dr. Smith, are you aware</p> <p>8       that the cohort studies that we've discussed today</p> <p>9       have also considered the migration hypothesis by</p> <p>10       considering the data on tubal ligation and ovarian</p> <p>11       cancer?</p> <p>12               MS. O'DELL: Object to the form.</p> <p>13       A. I need to look at those studies for the</p> <p>14       specific information. May I retrieve them?</p> <p>15       Q. (BY MR. JAMES) Sure. If I --</p> <p>16       A. Nope.</p> <p>17       Q. If I can refer you first to the Houghton</p> <p>18       WHI study.</p> <p>19       A. Sure. Okay, Gates.</p> <p>20               I need Gertig and I -- have you given</p> <p>21       me Gonzalez?</p> <p>22       Q. We have not marked Gonzalez.</p> <p>23       A. Okay. Then I will not look for it.</p> <p>24               (Examined exhibit.) Yes.</p>

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<p style="text-align: right;">Page 278</p> <p>1 Q. Okay. So are you aware that the cohorts 2 also included data on that hypothesis? 3 MS. O'DELL: Object to the form. 4 A. Now I am, yes. 5 Q. (BY MR. JAMES) Did you cite that data in 6 your report? 7 A. I did not. 8 Q. Earlier you discussed that in 9 acknowledging the Terry finding on tubal ligation 10 that you had considered the entire body of 11 literature, correct? 12 MS. O'DELL: Object to the form. 13 A. Yes. 14 Q. (BY MR. JAMES) And that's one of the 15 reasons that you discounted the Terry finding on the 16 tubal ligation migration issue, correct? 17 MS. O'DELL: Object to the form. 18 A. I didn't discount it. I think the 19 preponderance of all the literature on tubal 20 ligation overpowers a single or two or three reports 21 that do not find tubal ligation important, either 22 not statistically significant or impair prognosis -- 23 increase risk of ovarian cancer. 24 Q. (BY MR. JAMES) Would you weigh the cohort</p>	<p style="text-align: right;">Page 280</p> <p>1 Q. (BY MR. JAMES) And you didn't discuss any 2 of that data in your report, correct? 3 A. I did not. 4 Q. Discussing now where we left off, 5 Dr. Smith, the data on NSAIDs. 6 A. Yes. 7 Q. In your report, you acknowledge the 8 literature on NSAIDs and ovarian cancer risk as 9 inconsistent, correct? 10 A. Yes. And in its totality. 11 Q. And earlier in your report when you list 12 what you considered to be generally accepted 13 protective factors, you do not list NSAIDs, correct? 14 A. Correct. 15 Q. Is that because you believe that it's not 16 generally accepted that NSAIDs apply a protective 17 effect for ovarian cancer? 18 MS. O'DELL: Object to form. 19 A. I don't think we have found the right 20 anti-inflammatories because I don't think we, as a 21 scientific community, do not understand the critical 22 points in inflammation and carcinogenesis and 23 disease progression. 24 So I believe in the future -- and I</p>
<p style="text-align: right;">Page 279</p> <p>1 data on this issue more heavily than the case 2 controlled data on this issue? 3 MS. O'DELL: Object to the form. 4 A. No. 5 Q. (BY MR. JAMES) Would you consider the 6 data on equal footing? 7 MS. O'DELL: Object to the form. 8 A. I con- -- I can consider all of these 9 individual studies equally. 10 Yes. I consider the case control 11 if -- just because it's a case control study about 12 effects of tubal ligation compared to a cohort 13 study, I don't think that weight is about pa- -- 14 recall of tubal ligation. 15 There -- there are studies on women 16 recalling whether they've had a surgical procedure 17 to end their fertility and they're pretty accurate 18 because it's pretty important to every woman. 19 Q. (BY MR. JAMES) Are you aware of any 20 prospective cohort data that supports the tubal 21 ligation migration hypothesis? 22 MS. O'DELL: Object to the form. 23 A. I cannot give you one off the top of my 24 head.</p>	<p style="text-align: right;">Page 281</p> <p>1 think this is critical -- in the future in 2 laboratory studies when we discern the actual 3 mechanisms of carcinogenesis, enzyme changes, 4 reactive oxygen species, DNA damage, aneuploidy, 5 malignancy, that we will be able to affect 6 inflammation and interrupt it in a -- in a very 7 progressive, protective way. I think that's coming, 8 and it's gonna come out of the lab. 9 Q. (BY MR. JAMES) Is it fair to say that 10 we're not there yet? 11 A. We're not there yet. 12 Q. Are you aware, as of today, with 13 doctors -- a doctor following a standard of care to 14 prescribe NSAIDs to decrease ovarian cancer risk? 15 A. Not in ovarian cancer. 16 Q. Would you agree that some types of 17 inflammation don't increase cancer risk? 18 MS. O'DELL: Object to the form. 19 A. I can think of examples of an acute single 20 inflammation episode that's been studied and not had 21 long-term cancer effects, but I think what we know 22 about cancer is that it is chronic inflammation, 23 repeated insult, the snowballing of the inflammatory 24 cascade inducing enzyme, changes reactive oxygen</p>

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<p>1 species, reactive nitrogen species and ultimately</p> <p>2 DNA alteration, inducing driver mutations and</p> <p>3 starting this thing going and then causing it to</p> <p>4 progress.</p> <p>5 Q. (BY MR. JAMES) Do you believe rheumatoid</p> <p>6 arthritis is associated with cancer?</p> <p>7 A. I have not reviewed that literature, and I</p> <p>8 cannot comment on that.</p> <p>9 Q. Can you think of any inflammatory</p> <p>10 conditions, as you sit here today, that are not</p> <p>11 associated with cancer?</p> <p>12 A. That are not associated with cancer?</p> <p>13 Q. Correct. Correct.</p> <p>14 MS. O'DELL: Object to the form.</p> <p>15 A. I haven't studied all inflammatory</p> <p>16 conditions.</p> <p>17 Q. (BY MR. JAMES) Did you look for</p> <p>18 genotoxicity studies in conducting your review in</p> <p>19 this case?</p> <p>20 A. Yes.</p> <p>21 Q. Okay. Did you review any?</p> <p>22 A. Yes.</p> <p>23 Q. Which ones?</p> <p>24 A. There is an article on nanoparticles and</p>	<p>1 asked to review his literature.</p> <p>2 Q. Do you know anything about his connection</p> <p>3 to this litigation?</p> <p>4 A. Yes, I do.</p> <p>5 Q. What do you know?</p> <p>6 A. I know that I suggested to Dr. Thompson</p> <p>7 that she get in touch with him and start reading his</p> <p>8 literature.</p> <p>9 Q. So were you the first point of contact</p> <p>10 between plaintiffs' counsel and Dr. Saed?</p> <p>11 A. I was the name. I was the person that</p> <p>12 gave them his name.</p> <p>13 Q. And how did you know Dr. Saed again?</p> <p>14 A. I don't know him. I just read his papers.</p> <p>15 Q. How did you become --</p> <p>16 A. I think they're good.</p> <p>17 Q. How did you become familiar with him or</p> <p>18 aware of him, just through his papers?</p> <p>19 A. Through his papers and looking at</p> <p>20 inflammation in ovarian cancer and reading GY --</p> <p>21 he's published in GY Oncology before. I just knew</p> <p>22 his paper. Maura Fletcher [sic, Nicole] who's in</p> <p>23 his lab, I think I saw her papers first.</p> <p>24 Q. Do you know Fletcher?</p>
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<p>1 talc. There is -- and I cannot remember the name of</p> <p>2 the author for the life of me. I can see the</p> <p>3 heading and there is a growing body of evidence on</p> <p>4 the role inflammation plays in the development of</p> <p>5 ovarian cancer.</p> <p>6 And their initial papers are more</p> <p>7 about oxidative stress in the pathogenesis of</p> <p>8 ovarian cancer. A group at Wayne State University</p> <p>9 have been looking at this for several years.</p> <p>10 Q. Do you know Dr. Saed?</p> <p>11 A. I have never met him. I've just read his</p> <p>12 stuff.</p> <p>13 Q. Had you read his papers before you were</p> <p>14 retained as an expert in this litigation?</p> <p>15 A. Yes.</p> <p>16 Q. You had read his papers?</p> <p>17 A. Yes.</p> <p>18 Q. When did you read his papers?</p> <p>19 A. Just in the course of -- he's presented at</p> <p>20 SGO before.</p> <p>21 Q. Do you know when?</p> <p>22 A. I know he -- oh, I know he had an abstract</p> <p>23 in '17. I think he's been there before that. And</p> <p>24 then I went deep diving into his paper after I was</p>	<p>1 A. I don't know any of them. I don't know</p> <p>2 anybody in -- I don't know where Wayne State is.</p> <p>3 It's in Michigan somewhere. I don't know anybody</p> <p>4 there.</p> <p>5 Q. Do you know if plaintiffs' counsel had a</p> <p>6 litigation relationship with Dr. Saed before you</p> <p>7 identified Dr. Saed as someone they should contact?</p> <p>8 A. I don't know if they did, but they may</p> <p>9 have. I don't know that.</p> <p>10 Q. Do you know anything about the funding of</p> <p>11 his studies?</p> <p>12 A. I do not.</p> <p>13 Q. And when were you retained in this</p> <p>14 litigation, it was 2017?</p> <p>15 A. January of 2017 was the first time that</p> <p>16 they asked me to look at the literature.</p> <p>17 Q. I looked at your references in your</p> <p>18 materials considered list. I didn't see reference</p> <p>19 to an Endo-Capron study.</p> <p>20 Does that title ring any bells with</p> <p>21 you, Endo-Capron?</p> <p>22 A. I don't -- it does not ring any bells.</p> <p>23 Q. If that study and a body of other studies</p> <p>24 on genotoxicity are not listed in your references</p>

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<p style="text-align: right;">Page 286</p> <p>1 list or your materials considered list, may I 2 assume, then, that you didn't review those studies? 3 MS. O'DELL: Excuse me. I object to 4 the question. I think it's vague. If there's a 5 specific study you want to ask her about, then you 6 know she's happy to review it and comment if you ask 7 her questions, but to the degree you've referenced, 8 quote, "a body of literature," that may not be the 9 way Dr. Smith is aware of it. 10 I object to the question. 11 MR. JAMES: Speaking objection is 12 noted. You can answer the question. 13 MS. O'DELL: Objection is noted. 14 MR. JAMES: Your speaking objection is 15 noted. That you've been speaking all day. So thank 16 you. 17 A. Could you ask the question again? I'm so 18 lost. 19 Q. (BY MR. JAMES) Okay. Let's start with 20 the Endo-Capron study. 21 If the Endo-Capron study is not listed 22 in your materials considered or reference list, then 23 may I safely presume that you did not review that 24 study?</p>	<p style="text-align: right;">Page 288</p> <p>1 A. I would presume so. 2 Q. (BY MR. JAMES) Are you aware of any 3 studies that have reported inflammation, granulomas, 4 or foreign body reactions in the ovarian tissue of a 5 woman following her usage of talcum powder products? 6 MS. O'DELL: Object- -- 7 A. I -- 8 THE WITNESS: Sorry, were you saying 9 something? 10 MS. O'DELL: Give me just a moment 11 here. 12 A. I know of -- I do not know of a human 13 study with talc related granuloma. 14 Q. (BY MR. JAMES) With respect to your 15 Bradford Hill analysis, Dr. Smith, we have covered a 16 lot of that along the way today, and so I'm going to 17 jump around just a little bit in hopes of moving us 18 along. Okay? 19 A. Okay. 20 Q. So with regard to specificity, which is 21 one of the factors you've analyzed in your report, 22 correct? 23 A. Yes. 24 Q. Do you believe that factor was met here on</p>
<p style="text-align: right;">Page 287</p> <p>1 MS. O'DELL: Objection. It goes to -- 2 A. Do you know who the author is? 3 MS. O'DELL: Excuse me. Excuse me. 4 Object to the form. 5 A. I mean, do I know -- would I know it by an 6 authors' name or another name of Endo-Capron? 7 Does it stand for something? 8 Q. (BY MR. JAMES) If you have not listed the 9 study in your references or materials considered 10 list, then may I assume or presume that you did not 11 review that study? 12 MS. O'DELL: Object to the form. 13 A. I don't recognize that study. I -- 14 with -- I can't give you more information. 15 MS. O'DELL: It's -- 16 Q. (BY MR. JAMES) If you have reviewed -- 17 MR. JAMES: This is a very simple 18 question, Leigh. 19 Q. (BY MR. JAMES) If you have reviewed a 20 piece of literature, whether you've cited it, 21 considered it, or referred to it, it would be listed 22 somewhere in your references list or your materials 23 considered list, correct? 24 MS. O'DELL: Objection to form.</p>	<p style="text-align: right;">Page 289</p> <p>1 this body of literature? 2 A. I . . . I think the -- 3 Q. And I believe -- sorry, Doctor. 4 A. -- body of all the work cited here 5 supports that criteria. I don't think that's as 6 important as the consistency and the strength. 7 Q. We have discussed strength earlier today, 8 and I don't want to replot ground that we have 9 plowed, but, in your opinion, is the criteria of 10 strength met on this body of literature? 11 A. I believe that. 12 Q. Can you cite any study or scientific 13 literature that characterizes the association at 14 issue as an association that is strong? 15 MS. O'DELL: Object to the form. 16 A. The numbers are what they are and 17 statistically significant and clinically 18 significant. 19 Q. (BY MR. JAMES) Can you cite to a single 20 study that characterizes the odds ratio or 21 association as strong? 22 MS. O'DELL: Object to the form. 23 Q. (BY MR. JAMES) That's a "yes" or "no" 24 question.</p>

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<p>1 MS. O'DELL: Object to the form.</p> <p>2 A. I haven't read the word "strong" in those</p> <p>3 studies.</p> <p>4 Q. (BY MR. JAMES) Do you believe the</p> <p>5 criteria consistency is met?</p> <p>6 A. Oh, yes.</p> <p>7 Q. Do you acknowledge that there is an</p> <p>8 inconsistency with respect to the results based upon</p> <p>9 the design study -- correct?</p> <p>10 MS. O'DELL: Objection to the form.</p> <p>11 A. You mean the cohort studies?</p> <p>12 Q. (BY MR. JAMES) Yes. Do you acknowledge</p> <p>13 that there is an inconsistency between the results</p> <p>14 produced by the cohort studies as compared to the</p> <p>15 results produced by the case control studies?</p> <p>16 A. Individually, but not in the meta -- not</p> <p>17 with their inclusion in the meta-analyses.</p> <p>18 So you're looking at individual</p> <p>19 studies, but when they go into the whole stew pot it</p> <p>20 becomes statistically significant and consistent.</p> <p>21 Q. And that brings us back to the word of</p> <p>22 heterogeneity that we discussed a bit earlier in the</p> <p>23 Berge study.</p> <p>24 But do you understand that in the</p>	<p>1 study.</p> <p>2 Q. (BY MR. JAMES) We discussed already that</p> <p>3 in the Penninkilampi study the finding that they</p> <p>4 included in that study based upon cohort studies</p> <p>5 omitted the data from the Gates 2010 study, correct?</p> <p>6 MS. O'DELL: Object to the form.</p> <p>7 A. Correct. We have discussed that.</p> <p>8 Q. (BY MR. JAMES) Would you agree that a</p> <p>9 lack of data on dose response, in a hypothetical</p> <p>10 situation, would counter against a causal</p> <p>11 interpretation?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A. That is one of the factors that one</p> <p>14 considers in determining causality.</p> <p>15 Q. (BY MR. JAMES) Do you believe dose</p> <p>16 response is met on the body of literature here?</p> <p>17 A. On the epidemiologic da- -- data, it --</p> <p>18 their dose response is equivocal. Penninkilampi</p> <p>19 found dose response in the -- in the meta-analysis,</p> <p>20 whereas Berge didn't.</p> <p>21 Q. Let me finish, Doctor. I'm sorry.</p> <p>22 A. I think it's -- as I said in my report, it</p> <p>23 is very difficult, even if you look at -- so many</p> <p>24 studies did not look at frequency and duration.</p>
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<p>1 Berge study one of the detractors from the causal</p> <p>2 interpretation was the heterogeneity between study</p> <p>3 and design?</p> <p>4 Do you understand that?</p> <p>5 MS. O'DELL: Object to the form.</p> <p>6 A. They didn't quantitate heterogeneity like</p> <p>7 they did in the Penninkilampi study which actually</p> <p>8 quantitated heterogeneity on the Newhouse Ottawa</p> <p>9 Scale [sic, Newcastle], so I think it's better to</p> <p>10 look at that. And none -- none of the studies in</p> <p>11 Penninkilampi had an NOS score less than 5, which</p> <p>12 meant they didn't have to get rid of anything for</p> <p>13 lack of -- for -- because of heterogeneity, and the</p> <p>14 cohort studies were in there. So I think we have a</p> <p>15 better idea of assessment of heterogeneity in</p> <p>16 that -- in that study.</p> <p>17 Q. (BY MR. JAMES) Okay. And my question is:</p> <p>18 Do you acknowledge that in the Berge study, one of</p> <p>19 the reasons the authors of that study concluded that</p> <p>20 the caus- -- causal interpretation was not</p> <p>21 appropriate was because of the lack of consistency</p> <p>22 between study design?</p> <p>23 MS. O'DELL: Object to form.</p> <p>24 A. I agree with you that is a quote from that</p>	<p>1 For example, Gertig, one of the cohort</p> <p>2 studies is ever/never in 1982. But many of the</p> <p>3 other studies didn't look at dose, duration,</p> <p>4 frequency, and how do you -- how do you establish</p> <p>5 dose in pouring powder on your bottom.</p> <p>6 So I -- I am not surprised that it's</p> <p>7 been in the epidemiologic literature very difficult</p> <p>8 to establish clear dose response curves.</p> <p>9 Q. You mentioned the Gertig study in your</p> <p>10 answer, Dr. Smith.</p> <p>11 And do you understand that the Gertig</p> <p>12 study did look at frequency?</p> <p>13 A. I thought the Gertig study was the Nurses'</p> <p>14 study, and they asked in 1982 ever/never, single</p> <p>15 time, and they never queried again.</p> <p>16 Q. So you're unaware of the fact that the</p> <p>17 Nurses' Health study included information on</p> <p>18 frequency?</p> <p>19 MS. O'DELL: Objection; form.</p> <p>20 Misstates.</p> <p>21 A. Let me look at it. It's right on top.</p> <p>22 (Examined exhibit.) They were given</p> <p>23 one assessment, no daily, one to six times a week,</p> <p>24 less than once a week, on sanitary napkins, yes, no,</p>

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<p style="text-align: right;">Page 294</p> <p>1 one time.</p> <p>2 That's not -- that's not a decent</p> <p>3 frequency and duration. I'm sorry. You don't know</p> <p>4 how long. You ask it one time. You don't account</p> <p>5 for changes in practices. That's not valid.</p> <p>6 Q. (BY MR. JAMES) Do you acknowledge that</p> <p>7 frequency is a valid measure of dose response?</p> <p>8 MS. O'DELL: Object to the form.</p> <p>9 A. It's a measure of assessing dose response.</p> <p>10 Q. (BY MR. JAMES) Do you acknowledge</p> <p>11 duration is a measure of assessing dose response?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A. Yes.</p> <p>14 Q. (BY MR. JAMES) Are you aware that there</p> <p>15 are case control studies that have looked at</p> <p>16 duration and frequency and found no dose response?</p> <p>17 MS. O'DELL: Object to the form.</p> <p>18 A. Yes.</p> <p>19 Q. (BY MR. JAMES) And, in fact, the studies</p> <p>20 that -- those studies are cited in your Exhibit B,</p> <p>21 correct?</p> <p>22 A. These are only single case control studies</p> <p>23 in Exhibit B, and I looked at dose responses. I</p> <p>24 read through the studies, and they attempted to do</p>	<p style="text-align: right;">Page 296</p> <p>1 on my Exhibit B chart in the Comments section.</p> <p>2 Q. And so my question that I think I</p> <p>3 originally posed is: Do you consider those findings</p> <p>4 relevant to your opinions today?</p> <p>5 A. They are a component of my -- of genital</p> <p>6 talc use, so, yes, they are a component of my</p> <p>7 opinion.</p> <p>8 Q. Do you understand the data in those</p> <p>9 studies does not show an association between the use</p> <p>10 of talcum powder on condoms, diaphragms, and</p> <p>11 sanitary napkins in ovarian cancer?</p> <p>12 MS. O'DELL: Object to the form.</p> <p>13 A. Most -- most studies, when you broke them</p> <p>14 down, they lost -- they did not have statistical</p> <p>15 significance. Your statement is correct.</p> <p>16 (Discussion off the record.)</p> <p>17 MR. SILVER: Could we go off the</p> <p>18 record?</p> <p>19 THE VIDEOGRAPHER: Going off the</p> <p>20 record. The time is 6:05 p.m.</p> <p>21 (A recess was taken from 6:05 p.m.</p> <p>22 to 6:16 p.m.)</p> <p>23 THE VIDEOGRAPHER: Back on the record.</p> <p>24 The time is 6:16 p.m.</p>
<p style="text-align: right;">Page 295</p> <p>1 that.</p> <p>2 Q. You acknowledged that some of the dose --</p> <p>3 excuse me, some of the case control studies that you</p> <p>4 cited do not show dose response, correct?</p> <p>5 A. I would say the majority do not show dose</p> <p>6 response with a single epi case control studies.</p> <p>7 Q. Did you consider the findings in the</p> <p>8 studies that you cited and in other literature</p> <p>9 pertaining to the use of talcum powder on condoms,</p> <p>10 diaphragms, or sanitary napkins?</p> <p>11 A. No.</p> <p>12 Q. Why not?</p> <p>13 A. Well, the good people that make condoms</p> <p>14 eliminated talc exposure on condoms in the 1990s.</p> <p>15 That's a very smart move.</p> <p>16 And then you start breaking down sales</p> <p>17 of these populations into small enough groups that</p> <p>18 you lose the ability to have statistical</p> <p>19 significance.</p> <p>20 Q. Do you understand the number of articles</p> <p>21 that you've cited and discussed in your report do</p> <p>22 include -- include finding on odds ratios associated</p> <p>23 with sanitary napkins, diaphragms, and condoms?</p> <p>24 A. Right. And I -- and I put some of those</p>	<p style="text-align: right;">Page 297</p> <p>1 MR. JAMES: Dr. Smith, thank you for</p> <p>2 your time. That's all the questions I have for now.</p> <p>3 THE WITNESS: Thank you.</p> <p>4 EXAMINATION</p> <p>5 BY MR. KLATT:</p> <p>6 Q. Dr. Smith, my name is Mike Klatt --</p> <p>7 A. Hi.</p> <p>8 Q. -- and I represent Imerys Talc America.</p> <p>9 Do you know what Imerys Talc America</p> <p>10 is?</p> <p>11 A. Yes.</p> <p>12 Q. What are they?</p> <p>13 A. They are -- own the mines from which the</p> <p>14 talc is mined.</p> <p>15 Q. Do you know what years they owned the</p> <p>16 mines from which the talc is mined and used in the</p> <p>17 Johnson &amp; Johnson talc-based body powder product?</p> <p>18 A. I know it's more recent, but I don't know</p> <p>19 the exact dates.</p> <p>20 Q. Do you know who owned the mines before</p> <p>21 Imerys owned them?</p> <p>22 A. Lusignac, which I think was J&amp;J.</p> <p>23 Q. No, Lusignac is Imerys, my client.</p> <p>24 A. Oh, is Imerys. Okay.</p>

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<p style="text-align: right;">Page 298</p> <p>1 Q. So who owned it before Lusignac and 2 Imerys? Do you know? 3 A. J&amp;J, I believe. 4 Q. Okay. I'm gonna skip around because a lot 5 of ground's been covered today -- 6 A. Okay. 7 Q. -- and I just have follow-ups on a bunch 8 of different areas, so -- 9 A. Okay. 10 Q. -- I'll be skipping from subject to 11 subject, and it's pretty random here. 12 You said earlier today that you knew 13 Dr. Hal Lawrence with ACOG? 14 A. Yes. 15 Q. If you communicate with Dr. Hal Lawrence, 16 or anybody else outside of this litigation, on the 17 subject of talc and ovarian cancer, are you gonna 18 disclose to them that you're a paid expert for 19 plaintiffs in the litigation? 20 BY MS. O'DELL: Object to the -- 21 A. No. 22 MS. O'DELL: Object to the form. 23 A. No. And I haven't talked to Dr. Lough- -- 24 Lawrence in 40 years.</p>	<p style="text-align: right;">Page 300</p> <p>1 looking at as the next exhibit, 28. If you can 2 please, Dr. Smith, put this sticker on here. 3 (Deposition Exhibit 27 and 28 marked 4 for identification.) 5 Q. (BY MR. KLATT) Have you read Dr. Hopkins 6 multiday deposition where he was questioned about 7 what you're looking at right now, Exhibit 28? 8 A. I have not read it in detail. 9 Q. Have you read Ms. Pier's deposition where 10 she was questioned about Exhibit 27? 11 A. I have not read it in detail. 12 Q. Do you know that Exhibit 27 and 28 that 13 you're looking at are attorney created charts? 14 MS. O'DELL: Objection; misrepresents 15 the record. 16 MR. KLATT: Not at all. It's exactly 17 what happened. 18 MS. O'DELL: Objection. 19 A. I have another J&amp;J sample here from 20 3-3-87. You want to just -- 21 MR. JAMES: Objection; nonresponsive. 22 Q. (BY MR. KLATT) Have you read Dr. Hopkins 23 multiday deposition that resulted in the creation of 24 Exhibit 28 --</p>
<p style="text-align: right;">Page 299</p> <p>1 Q. (BY MR. KLATT) Okay. But I'm just asking 2 in the future. 3 Q. (BY MR. KLATT) You understand that Imerys 4 tests talc of competitors. It tests talc from mines 5 that are never used for body powder. It tests talc 6 from portions of mines that are never used for any 7 purpose. 8 You can't tell me that any of these 9 samples ended up in Johnson &amp; Johnson Body Powder, 10 can you? 11 MS. O'DELL: Objection to the form; 12 misstates the evidence, misleading, mischaracterizes 13 the document. 14 A. (Examined document.) 9-9-1975, Johnson's 15 Baby Powder anthophyllite and tremolite on the 28. 16 Q. (BY MR. KLATT) And do you have any proof 17 that Imerys owned the mines that that sample came 18 from at the time it was tested? 19 MS. O'DELL: Objection. 20 A. I don't. 21 Q. (BY MR. KLATT) I'm sorry? 22 MS. O'DELL: Objection. 23 A. I don't know when Imerys bought the mine. 24 Q. (BY MR. KLATT) And let's mark what you're</p>	<p style="text-align: right;">Page 301</p> <p>1 (Speaking simultaneously.) 2 A. No. 3 Q. (BY MR. KLATT) -- or Ms. -- 4 A. Not in detail -- 5 Q. -- or Ms. Pier's -- 6 A. -- no. 7 Q. -- deposition -- 8 MS. O'DELL: Let him finish. 9 Q. (BY MR. KLATT) -- that resulted in the 10 creation of Exhibit 27 to your deposition? 11 A. Not in detail. 12 Q. Do you understand that they had 13 explanations why each of those items that you're 14 looking at had nothing to do with any asbestos in 15 Johnson &amp; Johnson Baby Powder? 16 MS. O'DELL: Objection. 17 A. I did not know that. 18 Q. (BY MR. KLATT) And if you were being 19 objective, you would weigh their explanations in 20 contrast to Dr. Longo's testimony that you're just 21 accepting at face value, correct? 22 MS. O'DELL: Objection; misstates the 23 record. 24 A. I think there are three different</p>

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<p>1 determinations.</p> <p>2 Q. (BY MR. KLATT) Well, you're just assuming</p> <p>3 what Dr. Longo found was valid, correct?</p> <p>4 MS. O'DELL: Objection. An expert is</p> <p>5 allowed to rely on another expert.</p> <p>6 You may answer the question if you</p> <p>7 understand.</p> <p>8 THE WITNESS: An expert is allowed to</p> <p>9 what?</p> <p>10 MS. O'DELL: To rely on the findings</p> <p>11 of another expert as counsel knows.</p> <p>12 A. I have no reason to doubt Dr. Longo's</p> <p>13 technique.</p> <p>14 Q. (BY MR. KLATT) Do you know anything about</p> <p>15 his technique?</p> <p>16 A. I have read it in his report, but I don't</p> <p>17 remember off the top of my head.</p> <p>18 Q. Have you -- do you have any expertise</p> <p>19 yourself in how to test a product to see whether</p> <p>20 there's asbestos in it?</p> <p>21 A. Only in the broadest general TEM, SEM, XRD</p> <p>22 case. I don't know how to perform any of those.</p> <p>23 Q. But let's -- you would agree with me</p> <p>24 that you accept -- you don't know Dr. Longo</p>	<p>1 MS. O'DELL: Objection. Incomplete --</p> <p>2 Q. (BY MR. KLATT) -- body powders, correct?</p> <p>3 MS. O'DELL: Excuse me. Objection;</p> <p>4 incomplete hypothetical. The Court will not make</p> <p>5 findings of fact. That's a jury's job and counsel</p> <p>6 knows that.</p> <p>7 MR. KLATT: Absolutely not. This</p> <p>8 court can exclude that evidence under Daubert, and</p> <p>9 you know it.</p> <p>10 MS. O'DELL: That's not a finding of</p> <p>11 fact, and you know that. End of story.</p> <p>12 MR. KLATT: But they can find that the</p> <p>13 methodology used is inadequate to show that there's</p> <p>14 asbestos in this product.</p> <p>15 MS. O'DELL: Which is not what you</p> <p>16 just said, and you know that, so it misstates the</p> <p>17 process.</p> <p>18 (Speaking simultaneously.)</p> <p>19 MR. JAMES: Ms. O'Dell --</p> <p>20 Q. (BY MR. KLATT) Well, let me ask you</p> <p>21 this --</p> <p>22 MR. JAMES: -- make your objections</p> <p>23 and let the record proceed.</p> <p>24 Q. (BY MR. KLATT) If the judge in this</p>
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<p>1 personally, correct?</p> <p>2 A. Not at all.</p> <p>3 Q. And you know nothing about his background</p> <p>4 or qualifications, correct?</p> <p>5 A. I have not --</p> <p>6 MS. O'DELL: Objection.</p> <p>7 A. -- studied his CV.</p> <p>8 Q. (BY MR. KLATT) But you were willing to</p> <p>9 accept his conclusions about asbestos being in body</p> <p>10 powder at face value, but you didn't even bother to</p> <p>11 look at the explanations that Dr. Hopkins from</p> <p>12 Johnson &amp; Johnson or Ms. Pier from Imerys gave that</p> <p>13 asbestos isn't in body powder --</p> <p>14 MS. O'DELL: Objection --</p> <p>15 Q. (BY MR. KLATT) -- correct?</p> <p>16 MS. O'DELL: Objection to the form.</p> <p>17 Misstates the record.</p> <p>18 A. I have not read their depositions.</p> <p>19 Q. (BY MR. KLATT) If this court were to</p> <p>20 determine when it examines the evidence that</p> <p>21 Dr. Longo's testing does not show asbestos in</p> <p>22 Johnson &amp; Johnson Body Powder, you would have no</p> <p>23 basis -- other basis to say that there is asbestos</p> <p>24 in Johnson &amp; Johnson --</p>	<p>1 case --</p> <p>2 MS. O'DELL: The record --</p> <p>3 MR. JAMES: That's the way it's</p> <p>4 supposed to work.</p> <p>5 Q. (BY MR. KLATT) If the judge in this case</p> <p>6 concludes that Dr. Longo's methodology is inadequate</p> <p>7 to show that asbestos is in Johnson &amp; Johnson Body</p> <p>8 Powder, then you have no basis to say that it is,</p> <p>9 correct?</p> <p>10 MS. O'DELL: Objection to the form.</p> <p>11 Misstates the record.</p> <p>12 A. I'd have to think about that.</p> <p>13 Q. (BY MR. KLATT) Are Exhibit 27 and 28 and</p> <p>14 Dr. Longo's testing the only documents you're</p> <p>15 relying on regarding asbestos being in Johnson &amp;</p> <p>16 Johnson Body Powder products?</p> <p>17 MS. O'DELL: Objection to form.</p> <p>18 A. No. There is the Blount deposition</p> <p>19 that --</p> <p>20 Q. (BY MR. KLATT) Do you know whether that</p> <p>21 has anything to --</p> <p>22 MS. O'DELL: Let her finish, please,</p> <p>23 sir.</p> <p>24 Q. (BY MR. KLATT) I'm sorry. Go ahead.</p>

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<p>1 MS. O'DELL: Let her finish.</p> <p>2 Go ahead.</p> <p>3 A. -- that identified asbestos in Baby</p> <p>4 Powder, Johnson's -- the -- that she identified as</p> <p>5 Johnson's Baby Powder.</p> <p>6 Q. (BY MR. KLATT) Do you know whether that</p> <p>7 Baby Powder --</p> <p>8 MS. O'DELL: Let her -- I don't think</p> <p>9 she's done.</p> <p>10 Q. (BY MR. KLATT) -- was supplied by Imerys?</p> <p>11 MS. O'DELL: I don't think she --</p> <p>12 she's done.</p> <p>13 A. I haven't finished thinking. I cannot</p> <p>14 think of another example at the top of -- off my</p> <p>15 head at this hour.</p> <p>16 Q. (BY MR. KLATT) Do you know whether</p> <p>17 Dr. Blount's finding of asbestos that you just</p> <p>18 referred to involved talc supplied by Imerys?</p> <p>19 A. As I answered previously, I do not know</p> <p>20 when Imerys assumed ownership of those mines.</p> <p>21 Q. So you can't tell the Court whether</p> <p>22 Dr. Blount's testing was testing talc from Imerys or</p> <p>23 not, correct?</p> <p>24 MS. O'DELL: Objection to form.</p>	<p>1 for a second. I think I'm done. I just need to</p> <p>2 look back over my notes.</p> <p>3 THE VIDEOGRAPHER: Going off the</p> <p>4 record. The time is 7:06 p.m.</p> <p>5 (Ms. Brown left the room.)</p> <p>6 (A recess was taken from 7:06 p.m.</p> <p>7 to 7:39 p.m.)</p> <p>8 THE VIDEOGRAPHER: Back on the record.</p> <p>9 The time is 7:39 p.m.</p> <p>10 MR. KLATT: I'm done with my</p> <p>11 questioning, subject to any follow-up, so . . .</p> <p>12 EXAMINATION</p> <p>13 BY MS. O'DELL:</p> <p>14 Q. Dr. Smith, I've got a few questions for</p> <p>15 you.</p> <p>16 A. Okey-doke.</p> <p>17 Q. I know it's been a long day so I'll be</p> <p>18 brief.</p> <p>19 You were asked a series of questions</p> <p>20 about the presence of asbestos in Johnson's Baby</p> <p>21 Powder and Shower to Shower.</p> <p>22 Do you remember those questions?</p> <p>23 A. I remember I was asked them.</p> <p>24 Q. Good answer to not a very specific</p>
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<p>1 A. I cannot.</p> <p>2 MS. O'DELL: Misstates the record.</p> <p>3 Q. (BY MR. KLATT) You're charging \$600 an</p> <p>4 hour; is that correct?</p> <p>5 A. I am.</p> <p>6 Q. Is that for all work you're doing in the</p> <p>7 case, including testimony, whether it's in a</p> <p>8 deposition or in a court of law?</p> <p>9 A. I believe there's a flat daily rate. I'm</p> <p>10 not sure about this, but I believe that a flat daily</p> <p>11 rate of 800 hours in one day is only \$5,000. That</p> <p>12 was an exaggeration. I'm trying to show that I've</p> <p>13 retained my sense of humor.</p> <p>14 Q. I think what you were saying is that if</p> <p>15 testimony lasted all day there would be a flat rate</p> <p>16 of \$5,000 --</p> <p>17 A. Correct.</p> <p>18 Q. -- is that correct?</p> <p>19 But if it's broken down by an hourly</p> <p>20 basis, whether you're doing reading or testifying,</p> <p>21 it's all \$600 an hour?</p> <p>22 A. That -- I agree with that.</p> <p>23 Q. Okay.</p> <p>24 MR. KLATT: Can we go off the record</p>	<p>1 question.</p> <p>2 Don't remember the specific questions,</p> <p>3 but you were asked about those topics?</p> <p>4 A. Yes.</p> <p>5 Q. And let me show you what I'm marking as</p> <p>6 Exhibit 29, which is Dr. Longo's report.</p> <p>7 (Deposition Exhibit 29 marked for</p> <p>8 identification.)</p> <p>9 Q. (BY MS. O'DELL) Are you, in part, relying</p> <p>10 on Dr. Longo's testing and his findings of the</p> <p>11 presence of asbestos in historical samples of</p> <p>12 Johnson's Baby Powder and Shower to Shower?</p> <p>13 A. Yes.</p> <p>14 Q. And from your review of Dr. Longo's</p> <p>15 report, he found -- did he find asbestos in a number</p> <p>16 of samples?</p> <p>17 A. He found --</p> <p>18 MR. JAMES: Objection; leading.</p> <p>19 A. He found asbestos in 66 percent of the</p> <p>20 samples he tested.</p> <p>21 Q. (BY MS. O'DELL) And did he test samples</p> <p>22 from a time period of the 1960s into the 1990s?</p> <p>23 MR. JAMES: Objection; leading.</p> <p>24 MR. KLATT: Object to form.</p>

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<p style="text-align: right;">Page 310</p> <p>1 A. Yes. And memory serves the last date on 2 his report was 2000, but there was a chart that I 3 saw. 4 Q. (BY MS. O'DELL) Is -- is -- what other -- 5 and you would defer to Dr. Longo on the testing 6 methodology that's appropriate for identifying 7 asbestos in Johnson's Baby Powder and Shower to 8 Shower? 9 MR. JAMES: Objection; form. 10 A. Yes. 11 Q. (BY MS. O'DELL) Would you also -- well, 12 strike that. 13 Did Dr. Longo also test for the 14 presence of fibrous talc? 15 A. He did. 16 MR. JAMES: Objection; form. 17 Q. (BY MS. O'DELL) Did he -- were there -- 18 what do you recall about Dr. Longo's findings 19 regarding fibrous talc? 20 A. I believe the vast majority of his samples 21 had fibrous talc. If memory serves, there's only 22 one sample in which he could not demonstrate fibrous 23 talc. 24 Q. And -- and you -- would you defer to</p>	<p style="text-align: right;">Page 312</p> <p>1 fibers. 2 And the now labeled Exhibit 27 by Pier 3 from -- deposition of Pier had Johnson &amp; Johnson 4 sample demonstrating chrysotile and tremolite. 5 Q. And is there also published literature 6 that -- in addition to Dr. Blount that reports 7 finding asbestos in cosmetic powders? 8 A. Yes. Those references are listed in the 9 very first sentence of my section on asbestos in my 10 report on page 18. 11 Q. And are you referring to -- 12 A. Cralley. 13 Q. Is that -- would you spell that for the 14 record? 15 A. C-r-a-l-l-e-y is the first author. 68. 16 Do you want me to pull all these 17 studies and go through here for you? 18 Q. No. 19 Would it be fair to say that in 20 addition to Dr. Longo's testing and the evidence 21 that you've referenced in regard to the -- to the 22 Hopkins chart and the Pier chart that there's 23 evidence in the published literature regarding the 24 presence of asbestos in talcum powder?</p>
<p style="text-align: right;">Page 311</p> <p>1 Dr. Longo on the methodology that's appropriate for 2 testing Johnson's Baby Powder and Shower to Shower 3 for the presence of fibrous talc? 4 MR. JAMES: Object to the form. 5 A. I would. 6 Q. (BY MS. O'DELL) Is there other evidence 7 that you relied on in considering the question of -- 8 of whether there is asbestos present in Johnson's 9 Baby Powder and Shower to Shower? 10 A. Yes. 11 Q. And -- and what is that evidence? 12 A. Blount found asbestos in Johnson &amp; 13 Johnson's Baby Powder. Her report is in 1991. Her 14 deposition specified that it wasn't just any talcum 15 powder; it was Johnson &amp; Johnson's. 16 Exhibits formerly known as 28, but now 17 known as -- no. Are you kidding? It's 28 again -- 18 showed tremolite, actinolite, and chrysotile -- 19 chryso- -- in Shower to Shower. 20 Do you want me to go through every one 21 of them, or just -- 22 Q. Not every one, but -- 23 A. Okay. But Johnson &amp; Johnson sent -- some 24 Johnson &amp; Johnson samples had identifiable asbestos</p>	<p style="text-align: right;">Page 313</p> <p>1 A. Yes. 2 MR. JAMES: Object to form. 3 Q. (BY MS. O'DELL) You were also asked 4 earlier today about your review of the literature 5 regarding the causal connection between exposure to 6 asbestos and ovarian cancer. 7 Do you recall those questions? 8 A. I do recall those questions. 9 Q. Was your review of the asbestos and 10 ovarian cancer literature comprehensive? 11 A. To the best of my ability. 12 Q. And you spoke earlier about the IARC 13 monogram regarding asbestos and fibrous talc or a 14 talcum asbestiform habit 100C -- you called that? 15 A. Yes. 16 Q. Do you -- 17 MR. JAMES: Objection; form. 18 Sorry, Leigh. 19 MS. O'DELL: Excuse me. 20 Q. (BY MS. O'DELL) Did you review all of the 21 monograph? Let me start there. 22 A. Yes. 23 Q. Did you review all of the articles that 24 are referenced in IARC's comprehensive review of</p>

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<p>1 asbestos?</p> <p>2 A. I read them.</p> <p>3 Q. Did --</p> <p>4 A. And other studies that have come out</p> <p>5 subsequent to IARC.</p> <p>6 Q. Did you attempt to review all the relevant</p> <p>7 literature regarding asbestos and ovarian cancer?</p> <p>8 A. I did.</p> <p>9 Q. Is that literature included on the</p> <p>10 materials considered list that I think is Exhibit C</p> <p>11 of your expert report?</p> <p>12 A. I believe all those references are in</p> <p>13 there.</p> <p>14 Q. Has IARC concluded that fibrous talc or</p> <p>15 talc in an asbestiform habit is a known human</p> <p>16 carcinogen?</p> <p>17 MR. JAMES: Object to form.</p> <p>18 A. Yes.</p> <p>19 Q. (BY MS. O'DELL) Now, I asked you just a</p> <p>20 moment ago about Exhibit C, the materials considered</p> <p>21 list, the -- the bigger list of literature that's --</p> <p>22 A. This (indicating)?</p> <p>23 Q. Yes -- included in your report.</p> <p>24 And did you review the materials that</p>	<p>1 "While there exists."</p> <p>2 Do you see that?</p> <p>3 A. Yes, I do.</p> <p>4 Q. And I think you and counsel for Johnson &amp;</p> <p>5 Johnson discussed this a little earlier. It says,</p> <p>6 "The potential for particulates to migrate from the</p> <p>7 perineum and vagina through the peritoneal cavity is</p> <p>8 indisputable."</p> <p>9 Did I read that correctly?</p> <p>10 A. You did.</p> <p>11 Q. Is that your opinion?</p> <p>12 A. Absolutely.</p> <p>13 Q. And counsel for Johnson &amp; Johnson</p> <p>14 suggested that that statement in this letter that's</p> <p>15 written by the FDA did not apply to talc and talc</p> <p>16 migrating through the upper genital tract.</p> <p>17 Do you recall that?</p> <p>18 MR. JAMES: Object to form and object</p> <p>19 to the mischaracterization.</p> <p>20 A. I recall that.</p> <p>21 MS. O'DELL: It was not a</p> <p>22 mischaracterization.</p> <p>23 Q. (BY MS. O'DELL) What does the next</p> <p>24 sentence say regarding the migration of perineal</p>
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<p>1 are listed on Exhibit C?</p> <p>2 A. I can't promise you that I've read every</p> <p>3 single word on every single study, but I have read</p> <p>4 the vast majority of them.</p> <p>5 Q. Let me --</p> <p>6 A. Greater than 90 percent.</p> <p>7 Q. Okay. Let me switch gears for a moment.</p> <p>8 You were asked a series of questions today about the</p> <p>9 FDA's response to the civil service petition. That</p> <p>10 was one topic.</p> <p>11 Do you recall that?</p> <p>12 A. Yes.</p> <p>13 Q. If you don't mind finding that and pulling</p> <p>14 it out. I think it's right here. It was Exhibit 8.</p> <p>15 A. Yes.</p> <p>16 Q. Do you recall that?</p> <p>17 A. Yes.</p> <p>18 Q. And if you will turn to page 5 of</p> <p>19 Exhibit 8. Just let me know --</p> <p>20 A. This is the FEC letter.</p> <p>21 Q. Yes.</p> <p>22 A. Yes.</p> <p>23 Q. And so if you'll look about a little more</p> <p>24 than halfway down the page, the paragraph beginning</p>	<p>1 talc?</p> <p>2 A. I was just getting ready to say it's the</p> <p>3 very next statement that they said: (Paraphrasing.)</p> <p>4 It is, therefore, plausible that perineal talc --</p> <p>5 other -- any -- they say (other particulate) can</p> <p>6 reach the endometrial cavity, fallopian tubes,</p> <p>7 ovaries, and peritoneum and may elicit a foreign</p> <p>8 body reaction, inflammatory response, but in some</p> <p>9 exposed women may progress to epithelial cancers.</p> <p>10 Q. And in terms of -- of -- of migration, let</p> <p>11 me also ask you -- just keep that in front of you,</p> <p>12 but I'm gonna pull out what's marked as Exhibit 19,</p> <p>13 the Langseth paper. If you see it, maybe you can</p> <p>14 help me.</p> <p>15 A. Yeah. I told you they're all messed up.</p> <p>16 Q. They -- they are.</p> <p>17 A. Here it is.</p> <p>18 Q. Okay. Great.</p> <p>19 And the -- in reference to Exhibit 19,</p> <p>20 earlier, counsel for J&amp;J suggested that the -- the</p> <p>21 IARC Working Group authored this paper.</p> <p>22 Do you recall that?</p> <p>23 A. I remember he -- this is from the Cancer</p> <p>24 Registry of Norway and Harvard and Montreal and</p>

80 (Pages 314 to 317)

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<p style="text-align: right;">Page 318</p> <p>1 Stockholm and Finland.</p> <p>2 Q. So this is not an official publication</p> <p>3 of -- of IARC. Fair?</p> <p>4 A. No, it is not.</p> <p>5 Q. And if you'll -- but the authors in this</p> <p>6 study, if you'll . . .</p> <p>7 A. Yeah. I see here where they mention the</p> <p>8 working group.</p> <p>9 Q. Yes. And, in fact, the authors of the --</p> <p>10 of the study, to be fair, are part of the working</p> <p>11 group. Is that . . .</p> <p>12 A. Correct.</p> <p>13 Q. And if you'll look at page 1 of Exhibit 19</p> <p>14 and if you'll -- the left-hand column, the -- it's</p> <p>15 the next to the last paragraph toward the end of the</p> <p>16 page, does the authors of the Langseth conclude that</p> <p>17 talc particles can migrate to the vagina to the</p> <p>18 peritoneal cavity and ovaries?</p> <p>19 A. They document asbestos fibers -- well,</p> <p>20 first they say: (Paraphrasing.) It's known that</p> <p>21 particles and fibres that enter the body can migrate</p> <p>22 to distant organs. Asbestos fibres that are found</p> <p>23 in the ovaries exposed to asbestos, analogously</p> <p>24 following perineal application, talc part--</p>	<p style="text-align: right;">Page 320</p> <p>1 the studies, I will cite S-j-ö-r-s-e-n, et al., Egli</p> <p>2 and Newton, et al., Hunes, Zerm-- a Greek study</p> <p>3 with the e-r.</p> <p>4 Q. Why don't you spell it for us?</p> <p>5 A. Why don't I look at my bibliography. It's</p> <p>6 gotta be the last one --</p> <p>7 THE VIDEOGRAPHER: We need to</p> <p>8 change --</p> <p>9 A. -- if they're in alphabetical order.</p> <p>10 THE VIDEOGRAPHER: -- the disk, like</p> <p>11 now, so if we can go off the record.</p> <p>12 MS. O'DELL: I'm sorry. I didn't hear</p> <p>13 you.</p> <p>14 THE VIDEOGRAPHER: The disk, I need to</p> <p>15 change it out. It finished a little earlier, so let</p> <p>16 me swap it out.</p> <p>17 MS. O'DELL: Can she finish her answer</p> <p>18 or . . .</p> <p>19 THE VIDEOGRAPHER: No because I have</p> <p>20 to switch it out. Sorry.</p> <p>21 (A recess was taken from 7:56 p.m.</p> <p>22 to 8:00 p.m.)</p> <p>23 THE VIDEOGRAPHER: This marks the</p> <p>24 beginning of disk 5. Back on the record. The time</p>
<p style="text-align: right;">Page 319</p> <p>1 particles can migrate from the vagina to the</p> <p>2 peritoneal cavity and ovaries. A majority of women</p> <p>3 experience retrograde menstruation. And this</p> <p>4 also -- this suggests a mechanism by which talc</p> <p>5 particles can travel through the female reproductive</p> <p>6 tract to the ovaries.</p> <p>7 Q. Is this part of the evidence that you</p> <p>8 relied on in supporting your opinion that talc</p> <p>9 particles applied to the -- to the perineal area can</p> <p>10 migrate to the upper genital tract, including the</p> <p>11 ovaries?</p> <p>12 A. Yes, and the research that these</p> <p>13 statements are based on.</p> <p>14 Q. Yes. And what other evidence do you rely</p> <p>15 on to support your opinion that talc can migrate to</p> <p>16 the ovaries?</p> <p>17 A. I have a section called "Migration" in --</p> <p>18 in my report. While I'm finding it, I'll start with</p> <p>19 the multiple human studies, which I weight more</p> <p>20 heavily -- or influenced me more strongly than</p> <p>21 studies in rodents that have shown particulate</p> <p>22 matter passing from the perineum into the peritoneal</p> <p>23 cavity.</p> <p>24 And -- and as I'm looking through all</p>	<p style="text-align: right;">Page 321</p> <p>1 is 8:00 p.m.</p> <p>2 Q. (BY MS. O'DELL) Dr. Smith, before we had</p> <p>3 to change the videographic tape, I had asked you</p> <p>4 what evidence you rely on to support your opinion</p> <p>5 that talc migrates from the perineum to the ovaries,</p> <p>6 and you were walking us through that.</p> <p>7 So why don't you just take a step back</p> <p>8 and --</p> <p>9 A. Did you get the reading from Langseth on</p> <p>10 the tape?</p> <p>11 Q. I think we got that. Assume we got that</p> <p>12 and then go from there.</p> <p>13 A. Okay. So there are a number of papers</p> <p>14 that look at migration of particulates.</p> <p>15 First, talc was identified deeply</p> <p>16 embedded in the ovaries, 1971 by Henderson.</p> <p>17 Egli and Newton had flushed carbon</p> <p>18 particles from the vaginal vault and that came out</p> <p>19 in the peritoneal cavity. These patients generally</p> <p>20 who were coming to abdominal surgery in some period</p> <p>21 of time, same day, next day, up to four days in</p> <p>22 these studies.</p> <p>23 And so this -- particulates would be</p> <p>24 placed in the vagina, not propelled, but placed in</p>

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<p style="text-align: right;">Page 322</p> <p>1 the vagina, and then the peritoneal cavity was  2 entered, washed to see if those particulates are  3 there. So Egli and Newton did carbon particles.  4 Sjösten did glove powder.  5 There are studies from K-u-n-z, looks  6 at micronized albumin particles placed in the vagina  7 that are transported.  8 There's a recent study by Zermanitokis  9 [sic] -- you have the spelling -- that looks at  10 tubal transport. And the great thing about that  11 study is that you can pass particles and demonstrate  12 them by ultrasonography and actually live-action  13 watch them go through the tube and study tubal  14 motal- -- motility as they go towards the dominant  15 ovarian part -- particle.  16 All these particles, a wide range of  17 studies from very small particles to larger  18 particles, the majority of them were approximating  19 sperm size, which is, in length, 5 microns.  20 So I looked at all these studies and  21 conclude that migration is real. There's -- a  22 female genital tract is the path to the peritoneal  23 cavity.  24 Dr. Woodruff gave his presidential</p>	<p style="text-align: right;">Page 324</p> <p>1 cavity, particulates of similar size, larger and  2 smaller, have been demonstrated to do that. These  3 are not motile; they're not flagellated. A particle  4 can go from outside to inside.  5 There's no reason why talc shouldn't  6 do it, and certainly we've seen talc deeply embedded  7 in the ovary suggesting that that's how it got  8 there.  9 Q. (BY MS. O'DELL) In fact, the evidence is  10 so strong the FDA has concluded it's indisputable.  11 MR. KLATT: Objection to form.  12 Q. (BY MS. O'DELL) Has the FDA concluded  13 that it's indisputable that talc can migrate from  14 the perineum to the upper genital tract?  15 MR. JAMES: Object to form.  16 Mischaracterizes the letter.  17 MR. KLATT: Misstates the testimony.  18 A. I think indisputable is the word that --  19 that Dr. Musser, deputy director for scientific  20 operations, Center for Food Safety and Applied  21 Nutrition, used in his letter to Dr. Epstein.  22 "The potential for particulates to  23 migrate from the peritoneum [sic] and vagina to the  24 peritoneal cavity is indisputable." That's the word</p>
<p style="text-align: right;">Page 323</p> <p>1 address in 1979 talking about ovarian cancer  2 resulting from unknown agents transversing the  3 vagina, cervix, endometrium, fallopian tube, into  4 the peritoneal cavity, surrounding the uterus and  5 inciting ovarian cancer.  6 I think we're seeing in in vitro  7 studies in the lab, as we study inflammation in  8 ovarian cancers, we are seeing -- able to generate  9 these studies at a molecular level without hurting  10 women, but seeing what the effect of exposure to  11 talc is on normal epithelial cells, fallopian  12 tubes . . .  13 Q. Before you get so far into that -- I'm  14 gonna ask you about that in just a moment, but let  15 me just ask one question before we leave migration.  16 It is the ability of talc applied to the perineum to  17 migrate through the -- the genital tract to the  18 ovaries.  19 Is that a hypothesis?  20 MR. JAMES: Object to form.  21 A. I think it is something that happens. It  22 is -- it has been -- while I have not seen a paper  23 that demonstrates talc, per se, has been transported  24 through the internal genitalia and to peritoneal</p>	<p style="text-align: right;">Page 325</p> <p>1 he used.  2 Q. (BY MS. O'DELL) Okay. Let me ask you to  3 go back to the topic you were -- had moved on to. I  4 just wanted to finish migration, and you were  5 talking about inflammation.  6 A. Yes.  7 Q. What evidence is there that talcum powder  8 causes inflammation?  9 A. Well, when you go into -- when you go into  10 the laboratory, you don't have to use the broad  11 brush of inflammation. You can look at specific  12 biochemical production or responses of molecules  13 involved in that inflammatory cascade.  14 So Kahn showed that nanopart --  15 nanotalc particles stabilized TNF-alpha, which is a  16 tumor necrosis factor alpha in human macrophages,  17 which is one of the steps in the inflammatory  18 cascade.  19 In fact, he found that the smaller --  20 the smaller of the pol- -- particle, the more the  21 production of unstabilization of TNF-alpha as  22 opposed to larger pol- -- particles.  23 Saed has, through the 2000s, looked at  24 ovarian cancer cell lines upregulation of</p>

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<p style="text-align: right;">Page 326</p> <p>1 anti-inflammatory and pro-inflammatory enzymes in 2 products. And then -- and he's written -- has a new 3 book chapter on it with Nicole Fletcher and all the 4 people in his lab. 5 And then has recently had a paper 6 accepted that looks at the response of controls, 7 normal ovarian epithelium, fallopian tube 8 epithelium, normal, and three different cell lines 9 of ovarian epithelial cancer cells in response to 10 three different levels of -- of talc. 11 And looked at the production of 12 pro-inflammatory enzymes, decrease in 13 anti-inflammatory enzymes, increase in cell 14 proliferation, decrease in apoptosis, and induction 15 of single-nucleotide polymorphisms that are 16 associated with carcinogenesis. 17 Before we had one paper where a 18 researcher named Buzard had taken a memorialized 19 normal ovarian cell line, exposed it to 5 milligrams 20 per -- micrograms, I'm sorry, per milliliter to -- 21 of talc, talcum powder, and this is scientific grade 22 talc, this was not Johnson's Baby Powder -- and 23 induced malignancy, as measured by the criteria of 24 lack of adherence in semi-solid auger, which is a</p>	<p style="text-align: right;">Page 328</p> <p>1 at -- at exposed normal mesothelial cells and then 2 normal ovarian epithelial ovarian cells to both 3 asbestos and nonfibrous talc and found induction of 4 pro-inflammatory genes have -- with exposure to 5 these 2 carcinogens. 6 Here's another Saed. 7 I think that covers it pretty much. 8 Q. (BY MS. O'DELL) You asked earlier today 9 about I think the question was -- well, let me just 10 ask it this way: Is there a regulatory body that 11 shares your view that talcum powder can cause 12 ovarian cancer? 13 MR. JAMES: Object to form. 14 A. The Canadian EPA, CEPA, came out with 15 Health Canada, which is publishing under -- is in 16 it's discussion period where they cite the 17 literature and base -- and their conclusion is that 18 talcum powders -- I can paraphrase it. 19 Do you have a copy that I can read? 20 But they say that talcum powder is a 21 significant public health risk to women from 22 perineal exposure, but I -- off the top of my head, 23 I can't remember their conclusion to read to you. 24 Q. (BY MS. O'DELL) You also asked some</p>
<p style="text-align: right;">Page 327</p> <p>1 standard of maligat -- malignancy and; yet, she 2 didn't do anything with it. She didn't 3 cytologically evaluate it. She didn't -- she just 4 said, "I made it a malignant." 5 So we have an example of malignant 6 transformation that is documented by a pretty 7 reliable basis if you query -- I can't say that, but 8 she really didn't go far with it. 9 Saed is starting to really break it 10 down, and he had a really remarkable dose response 11 in vitro to 5, 50, or 100-microgram per mil talc in 12 his changes. 13 MR. KLATT: Object to the narrative 14 answer. 15 Q. (BY MS. O'DELL) Has -- in addition to the 16 Buzard paper you mentioned and Dr. Saed's work over 17 the last decade, have there been others that looked 18 at talc and -- in cell cult -- culture and found 19 evidence that talc produced inflammation? 20 MR. KLATT: Objection; 21 mischaracterization. 22 MR. JAMES: Join. 23 A. Oh, Shulka. I forgot that study. That's 24 a big one. Shulka -- Shulka, S-h-u-l-k-a, looked</p>	<p style="text-align: right;">Page 329</p> <p>1 questions today about the -- about ACOG. 2 Do you remember those questions about 3 ACOG and the societies -- 4 A. Um-hum. 5 Q. -- of which you're a member? 6 A. Um-hum. 7 Q. What's referred to as "The Green Journal," 8 I believe? 9 A. It's obstetrics and gynecology. It's the 10 journal of ACOG. 11 Q. And has -- recently have papers been 12 published regarding ovarian cancer and its -- excuse 13 me, and talcum powder causing -- well, let me strike 14 that and start over. 15 Have recently, in The Green Journal, 16 there have been a publication dealing with talcum 17 powder products causing a significant increase in 18 ovarian cancer? 19 A. I think what -- 20 MR. JAMES: Object to form. 21 A. I think what you're referring to is, you 22 know, the end of every year they -- they review a 23 lot of topics and it's, you know, top five articles 24 in preeclampsia and top five articles in</p>

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<p style="text-align: right;">Page 330</p> <p>1 endometriosis and there's Jason Wright wrote the top 2 five articles in ovarian cancer. 3 And I think -- I don't remember 4 whether they were ranked, but I know Number 4 on the 5 list was the Penninkilampi study, but that's -- I 6 don't know who decides that. I don't remember 7 reading how that was decided, but I know Jason 8 Wright wrote it. 9 Q. (BY MS. O'DELL) And is that something 10 that suggests that the -- the causal connection 11 between the use of genital talc and ovarian cancer 12 is becoming more well-known in the medical 13 community? 14 MR. JAMES: Objection to form. 15 MR. KLATT: Objection; leading. 16 Speculation. 17 A. I think both Canada Health and the flurry 18 of two publications in '18. There are other studies 19 that are ongoing and in various stage of analysis, 20 preparation, proof, shows that we're getting a lot 21 more interest in talc and its relationship to 22 ovarian cancer. And there is increasing concern in 23 the -- all over the world, but the studies I know of 24 are largely in the United States and Canada.</p>	<p style="text-align: right;">Page 332</p> <p>1 present in talcum powder in certain periods. 2 MR. JAMES: Object to form. 3 Q. (BY MS. O'DELL) Do you rely on IARC's 4 comprehensive review of the literature regarding the 5 carcinogenicity of chromium? 6 A. Yes. 7 Q. Did you review IARC's analysis of -- 8 A. Yes. I read that. That is the way I made 9 my assessment of whether or not they are toxic. 10 Q. And did you -- in the same way, did you 11 review IARC's Monograph in relation to nickel? 12 A. Yes. 13 Q. And do you rely on IARC's comprehensive 14 review of both the epidemiological literature, the 15 animal studies, and other evidence regarding the 16 carcinogenicity of nickel? 17 A. Yes. 18 Q. And -- 19 A. I didn't individually pull every one of 20 their papers. I just read IARC. 21 Q. And you relied on IARC's review of those 22 materials? 23 A. Yes. I have trusted them. If they say 24 nickel is a carcinogen at specific levels, then I</p>
<p style="text-align: right;">Page 331</p> <p>1 Q. (BY MS. O'DELL) Let me change topics just 2 for a minute. 3 You were asked questions throughout 4 the day, different points about the fragrance 5 chemicals that comprise the fragrance for -- 6 fragrances for Baby Powder and Shower to Shower. 7 Do you recall that? 8 A. I do recall that. 9 Q. Do you -- did you -- excuse me. 10 Do you defer to Dr. Crowley on his 11 examination of the specific characteristics of those 12 fragrance chemicals? 13 A. I was getting ready to say I defer -- 14 before you could finish your sentence. I defer to 15 Dr. Crowley on everything about fragrances. 16 Q. And do you -- I mean, your -- do you rely 17 on his opinions regarding the inflammatory, toxic, 18 and potential carcinogenic effect of the chemicals 19 in the fragrances for Baby Powder and Shower to 20 Shower? 21 A. Yes. I don't know anything about those 22 substances. 23 Q. You were also asked questions about the 24 heavy metals that had been demonstrated to be</p>	<p style="text-align: right;">Page 333</p> <p>1 have no intention of pulling all those papers and 2 studying them myself. 3 Q. And would the same be true of Cobalt? 4 A. Yes. 5 Q. I want to show you what I'm going to mark 6 as Exhibit 30, and this is a copy of the Berge 7 paper. It's the most up-to-date copy. 8 (Deposition Exhibit 30 marked for 9 identification.) 10 Q. (BY MS. O'DELL) So I've handed you 11 Exhibit 30. It's a copy -- 12 A. Um-hum. 13 Q. It's the most up-to-date copy of the Berge 14 paper. We had discussions today at different times. 15 I think that we had different Berge publications, 16 and so I want to mark the one that has been 17 published most recently. 18 A. Okay. This is -- we have previously 19 marked the e-Pub. This is the print. 20 Q. All right. And if you'll -- I have just 21 one question. 22 You were asked today or the suggestion 23 was made to you today that in Berge the study did 24 not demonstrate a dose response.</p>

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<p>1 Do you recall those questions?</p> <p>2 A. Yes.</p> <p>3 Q. And if you'll take a look at the next to</p> <p>4 last sentence of the abstract --</p> <p>5 A. Yes.</p> <p>6 Q. -- of Berge.</p> <p>7 Do you see that?</p> <p>8 A. Yes.</p> <p>9 Q. And, in fact, did Berge demonstrate a -- a</p> <p>10 dose response?</p> <p>11 A. He says it's a -- which appears to be</p> <p>12 limited, that -- okay.</p> <p>13 "Statistically significant association</p> <p>14 between general use of talc in ovarian cancer, which</p> <p>15 appears to be limited to serous carcinoma was</p> <p>16 suggestion of dose-response."</p> <p>17 Q. The . . .</p> <p>18 A. And he has a table of the duration</p> <p>19 frequency.</p> <p>20 Q. And is that table supportive of the fact</p> <p>21 that the studies show the -- a dose response or at</p> <p>22 least the trending of a dose response?</p> <p>23 A. Their -- the --</p> <p>24 MR. KLATT: Objection.</p>	<p>1 Q. Yeah. Have you been asked to look at any</p> <p>2 individual patients in order to render what's</p> <p>3 ter- -- referred to as a case specific opinion?</p> <p>4 A. No.</p> <p>5 Q. And is it -- would you be willing to do</p> <p>6 that if asked?</p> <p>7 A. No. I haven't thought about it.</p> <p>8 Q. Okay.</p> <p>9 A. I'd like to think about it before I accept</p> <p>10 any more responsibility.</p> <p>11 Q. Yeah.</p> <p>12 Does that in any way --</p> <p>13 A. At this hour -- at this hour of the</p> <p>14 deposition.</p> <p>15 Q. Does that in any way undermine or change</p> <p>16 your opinion that talcum powder products, Baby</p> <p>17 Powder and Shower to Shower cause ovarian cancer?</p> <p>18 A. No.</p> <p>19 MR. KLATT: Objection; leading.</p> <p>20 A. It doesn't change my mind.</p> <p>21 Q. (BY MS. O'DELL) And is that opinion based</p> <p>22 on your review of the totality of the literature as</p> <p>23 you've described in your report and in the materials</p> <p>24 that are cited not only within the report but also</p>
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<p>1 MR. JAMES: Object to form.</p> <p>2 A. His results -- his relative risks are 1.16</p> <p>3 for a duration. 1.05 for frequency. They are</p> <p>4 statistically significant with 1.07 to 1.26 for a</p> <p>5 duration. 1.04 to 1.07 confidence intervals. But</p> <p>6 his number of risk estimates are small, 12 and 7.</p> <p>7 Q. Okay. You . . .</p> <p>8 MR. JAMES: Leigh, if you're done with</p> <p>9 Exhibit 30, may I have a look at it, please.</p> <p>10 MS. O'DELL: Sure.</p> <p>11 A. I think -- from what I've seen, it looks</p> <p>12 pretty much the same.</p> <p>13 MR. JAMES: Thank you.</p> <p>14 Q. (BY MS. O'DELL) Let me ask you to --</p> <p>15 A. Except that chart is -- oh, yeah. It's in</p> <p>16 the other one. Down here. I think they're the same</p> <p>17 thing.</p> <p>18 Go ahead.</p> <p>19 Q. Doctor, you were asked a series of</p> <p>20 questions about individual patients and whether</p> <p>21 talcum powder can cause ovarian cancer in an</p> <p>22 individual patient.</p> <p>23 Do you remember those questions?</p> <p>24 A. Generally.</p>	<p>1 Exhibit C?</p> <p>2 MR. JAMES: Object to form.</p> <p>3 A. Yes. I -- I find the epidemiologic data</p> <p>4 and the consistency is so significant, and then the</p> <p>5 biochemical stuff, the skin would be coming out like</p> <p>6 gangbusters. Speaks to plausibility,</p> <p>7 experimentation, mechanism, and that's just very</p> <p>8 compelling.</p> <p>9 Q. (BY MS. O'DELL) And in terms of the</p> <p>10 opinions that you've expressed in your report, are</p> <p>11 those opinions based on the published literature and</p> <p>12 other data that you have referenced and relied on in</p> <p>13 your report?</p> <p>14 A. Yes.</p> <p>15 Q. Okay.</p> <p>16 A. All of that has been published and</p> <p>17 peer-reviewed.</p> <p>18 Q. Right.</p> <p>19 So the degree that there's new data</p> <p>20 coming out, you're not relying on sort of the hope</p> <p>21 of new data in the future to reach your opinions?</p> <p>22 A. No, I think I'm willing to commit and make</p> <p>23 my opinion. I -- I feel very excited that we</p> <p>24 have -- we will have opportunities as we understand</p>

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<p style="text-align: right;">Page 338</p> <p>1 this process, the therapeutic interventions at some 2 time. 3 Q. You were asked questions earlier today 4 about what you had done prior to litigation and what 5 you've done post litigation in terms of informing 6 your opinions in this case. 7 Did you know that talc and asbestos 8 are inflammatory prior to becoming involved in the 9 litigation? 10 A. Yes. 11 MR. JAMES: Object to form. 12 Q. (BY MS. O'DELL) Prior to the litigation, 13 did you know, based on your understanding of the 14 medical and scientific literature, that inflammation 15 creates a pro-carcinogenesis -- excuse me, 16 carcinogenic environment? 17 MR. JAMES: Object to form. 18 A. Yes. 19 Q. (BY MS. O'DELL) Prior to the litigation, 20 did you know, based on your review of the scientific 21 and medical literature, that inflammation was a 22 mechanism for epithelial ovarian cancer development 23 and progression? 24 MR. JAMES: Object to form.</p>	<p style="text-align: right;">Page 340</p> <p>1 Q. Are your opinions in this case outlined in 2 your deposition today as well as the report that 3 you've provided in this case? 4 A. Yes. 5 Q. And every time today when you have 6 referred to talcum powder products, have you been 7 referring to Johnson's Baby Powder and Shower to 8 Shower? 9 MR. JAMES: Object to form. 10 A. Except when specified otherwise. 11 Q. (BY MS. O'DELL) Okay. And then last 12 question. You were asked a series of -- or maybe 13 the last question. 14 You were asked a -- 15 A. I got so excited. 16 Q. We've got a series of questions about what 17 you tell your patients, and you -- 18 A. Um-hum. 19 Q. -- testified that you do not tell your 20 patients presently about the increased risk of 21 ovarian cancer with perineal talc use. 22 Do you recall that? 23 A. I do. 24 Q. Do you treat patients with ovarian cancer</p>
<p style="text-align: right;">Page 339</p> <p>1 A. Certainly the recent data is more 2 compelling, that has been postulated, and various 3 little snippets of data like some of Saed's stuff 4 and enzyme induction, stuff like that, has been 5 leading there. It's been growing. 6 Q. (BY MS. O'DELL) But you were aware of 7 that -- 8 A. Yeah, prior to -- 9 Q. -- in -- excuse me. You were aware of -- 10 A. -- prior to January of 2017. 11 Q. Okay. 12 MR. JAMES: Object to the form. 13 Q. (BY MS. O'DELL) Prior to litigation, did 14 you know that particles such as talc and asbestos 15 could migrate or be transported to the fallopian 16 tube and ovary from the perineum? 17 MR. JAMES: Object to the form. 18 A. Oh, yes. 19 Q. (BY MS. O'DELL) Prior to the litigation, 20 were you aware of scientific data and medical 21 literature demonstrating that talc as well as 22 asbestos could be exposed to the body through 23 inhalation? 24 A. Oh, yes.</p>	<p style="text-align: right;">Page 341</p> <p>1 at this time? 2 A. At the end of their life. 3 Q. Why do you not tell them about talc as 4 a -- as a cause of ovarian cancer? 5 A. It's too late. 6 Q. Why? 7 A. They're dying. 8 Q. And -- 9 A. There's nothing -- they failed all 10 therapy. If there was adequate therapy -- 11 Q. And it would be -- 12 A. -- to reverse it, then they wouldn't be my 13 patient. 14 Q. And it would be insensitive and wrong to 15 counsel a patient at that junction in their life -- 16 A. Um-hum. 17 Q. -- about a risk factor that they will have 18 no effect on their -- 19 A. They can't do anything about it. I don't 20 want to induce guilt. The horse is out of the barn. 21 They need pain control. 22 They need nausea control. 23 They need love, support. They need 24 their family, you know, their priest or spiritual</p>

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<p style="text-align: right;">Page 342</p> <p>1 leader. They need a lot of care, but they don't</p> <p>2 need to be told "This happened because you used</p> <p>3 powder" or, "Boy, if you hadn't" -- I don't know.</p> <p>4 That'd be just dumb.</p> <p>5 MS. O'DELL: I don't have any further</p> <p>6 questions, Dr. Smith. Thank you.</p> <p>7 I'm sure these -- one of these</p> <p>8 gentlemen will have some questions.</p> <p>9 MR. JAMES: We will.</p> <p>10 Are we taking five, Mike?</p> <p>11 MR. KLATT: Five minutes.</p> <p>12 MR. JAMES: Okay.</p> <p>13 MR. KLATT: We'll just need a time</p> <p>14 from the videographer.</p> <p>15 MR. JAMES: Okay.</p> <p>16 THE VIDEOGRAPHER: So let's -- are we</p> <p>17 going off?</p> <p>18 MR. KLATT: We don't need to go off.</p> <p>19 Just what's the time?</p> <p>20 THE VIDEOGRAPHER: 32 plus 16 prior,</p> <p>21 so it should be 48.</p> <p>22 MS. O'DELL: So I'm not sure what</p> <p>23 the -- I'm not sure what the calculation's being</p> <p>24 made.</p>	<p style="text-align: right;">Page 344</p> <p>1 powder.</p> <p>2 Q. (BY MR. JAMES) Are you aware of any</p> <p>3 scientific literature or studies that address</p> <p>4 whether the chemicals and the fragrances of talc</p> <p>5 powder cause ovarian cancer?</p> <p>6 A. I do not. I defer to Dr. Crowley.</p> <p>7 Q. Did you consider the body of literature,</p> <p>8 looking at whether talc is associated with other</p> <p>9 types of gynecological cancers?</p> <p>10 A. I did not --</p> <p>11 MS. O'DELL: Object to the form.</p> <p>12 A. I did not even search endometrial cancer,</p> <p>13 cervical cancer, vulvar cancer.</p> <p>14 Q. (BY MR. JAMES) Do you believe that body</p> <p>15 of literature would be relevant to the opinions</p> <p>16 you're offering today?</p> <p>17 A. It would be confirmatory, were it to</p> <p>18 exist.</p> <p>19 Q. Confirm --</p> <p>20 A. I don't know if it exists.</p> <p>21 Q. Sorry.</p> <p>22 Confirmatory to the extent that it</p> <p>23 revealed an association, correct?</p> <p>24 MS. O'DELL: Object to the form.</p>
<p style="text-align: right;">Page 343</p> <p>1 MR. SILVER: Let's go off the record</p> <p>2 so we can figure out the calculation because I think</p> <p>3 it's different that he . . .</p> <p>4 THE VIDEOGRAPHER: Going off the</p> <p>5 record. The time is 8:32 p.m.</p> <p>6 (A recess was taken from 8:32 p.m.</p> <p>7 to 8:43 p.m.)</p> <p>8 THE VIDEOGRAPHER: Back on the record.</p> <p>9 The time is 8:43 p.m.</p> <p>10 FURTHER EXAMINATION</p> <p>11 BY MR. JAMES:</p> <p>12 Q. Dr. Smith, good evening.</p> <p>13 A. Hi.</p> <p>14 Q. I have a few more questions for you.</p> <p>15 Okay?</p> <p>16 A. Okey-doke.</p> <p>17 Q. Are you aware of any studies or literature</p> <p>18 showing that the presence of heavy metals in</p> <p>19 cosmetic talc powders increases the risk of ovarian</p> <p>20 cancer?</p> <p>21 MS. O'DELL: Object to the form.</p> <p>22 A. I know that IARC calls those Class 1 --</p> <p>23 two of them Class 1 carcinogens. I don't know how</p> <p>24 much they influence the carcinogenicity of talcum</p>	<p style="text-align: right;">Page 345</p> <p>1 A. To the extent that it revealed an</p> <p>2 association if such literature exists.</p> <p>3 Q. (BY MR. JAMES) If the literature, looking</p> <p>4 at the association between talc and other</p> <p>5 gynecological cancers, did not support an</p> <p>6 association, would that impact the opinions you're</p> <p>7 offering today?</p> <p>8 MS. O'DELL: Object to the form.</p> <p>9 A. Probably not.</p> <p>10 Q. (BY MR. JAMES) Why is that?</p> <p>11 A. Because -- because of the lethality of</p> <p>12 ovarian cancer, we do much better curing endometrial</p> <p>13 and cervix cancer. Ovarian cancer is a real killer.</p> <p>14 Not that I want anybody to get cancer.</p> <p>15 Q. And I'm not sure that I understood your</p> <p>16 answer.</p> <p>17 A. Okay.</p> <p>18 Q. So -- and it may -- and it's probably on</p> <p>19 my part.</p> <p>20 But you said because of the?</p> <p>21 A. Lethality. Lethal.</p> <p>22 Q. Lethality? Lethality. Okay.</p> <p>23 A. Yeah, of ovarian cancer. It is unusual</p> <p>24 to -- it's unusual to find ovarian cancer at an</p>

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<p style="text-align: right;">Page 346</p> <p>1 early stage. It is unusual to cure ovarian cancer.  2 We have a pretty darn good -- well, it could be  3 better. We don't cure everybody. But we have a  4 pretty good track record with curing endometrial and  5 cervical cancer. Not that I want anybody to get  6 cancer, but we need to do everything to decrease the  7 incidence of ovarian cancer.  8 Q. If your opinion is that talc causes  9 ovarian cancer, would you believe that talc would  10 also cause cervical cancer?  11 A. I don't know that information.  12 MS. O'DELL: Objection; form.  13 A. Cervical cancer -- cervical cancer, in  14 all, except extremely rare incidents such as DES  15 exposure, which thank God we've gotten rid of, is --  16 a component of cervical cancer is human papilloma  17 virus, which is a necessary but insufficient  18 carcinogen. That is, this is your cumulative -- one  19 of your cumulative examples where you've got to have  20 the one of HPV, but then you need another punch.  21 You need another factor. You can't just have HPV to  22 cause cervical cancer.  23 I -- I can't think of any research  24 that -- in influence of talc usage in cervical</p>	<p style="text-align: right;">Page 348</p> <p>1 A. Okay. I haven't found any differences  2 between the two, except the page numbers.  3 Q. And Dr. Smith, if you could just look at  4 that abstract for me on the first page, please.  5 A. Yes.  6 Q. And you see at the bottom of the abstract  7 that -- the sentence that I asked you about earlier,  8 and discussed with you at some length, about the  9 heterogeneity issue.  10 Do you see that?  11 A. Yes.  12 Q. Okay. And you see there that the authors  13 of the Berge paper still conclude on Exhibit  14 Number 30 that a causal interpretation is not  15 warranted, correct?  16 MS. O'DELL: Objection; form.  17 A. It says, "The heterogeneity" -- they  18 didn't say it's not causal. They say the  19 heterogeneity results detract from a causal  20 interpretation, so that lowers the chance that  21 they're willing to make in a causal association. It  22 doesn't strike it out entirely.  23 Q. (BY MR. JAMES) And that language is  24 consistent with the language that we discussed</p>
<p style="text-align: right;">Page 347</p> <p>1 cancer. I don't think I've ever seen that paper.  2 Q. (BY MR. JAMES) Would you expect talc to  3 be associated with uterine cancer?  4 A. I've never seen that paper either. Taking  5 us back to Mr. -- is it Klatt? Menstruation  6 association -- I'm just -- I'm thinking, and I  7 shouldn't be thinking. I should -- I've never seen  8 that paper.  9 Q. Or body of papers, if such a body exists,  10 correct?  11 A. Or if such a body --  12 MS. O'DELL: Object to the form.  13 A. -- exists.  14 Q. (BY MR. JAMES) You would agree that if  15 talc migrates to the genital tract, that talc would  16 be exposed to tissues and organs along the way,  17 correct?  18 A. Yes.  19 Q. Okay. You discussed with your counsel  20 Exhibit Number 30, which is the most recent version  21 of the Berge paper, correct?  22 A. Yes. I have the -- I have the 24, but I  23 think this is good enough.  24 Q. And I'm gonna hand you back Exhibit 30.</p>	<p style="text-align: right;">Page 349</p> <p>1 earlier today, correct?  2 A. It is.  3 MS. O'DELL: Objection; form.  4 Q. (BY MR. JAMES) During counsel's  5 questions, you made references to literature or  6 studies that I think you characterized as "would be  7 coming out."  8 Is that terminology that I heard  9 correctly?  10 A. Yes.  11 Q. Okay. Are you aware of studies on the  12 talc ovarian cancer hypothesis that are works in  13 progress?  14 A. Yes.  15 Q. Okay. What are those studies?  16 A. Well, there's another epidemiologic study  17 cited in Health Canada by Traher -- Taher,  18 T-a-h-e-r, Mohamed Taher, and a whole bunch of other  19 people. That is another epidemiologic  20 meta-analysis.  21 Q. Are there any other studies that you're  22 aware of that pertain to the issues in this  23 litigation that are works in progress?  24 A. I think people all over are still actively</p>

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<p>1 looking at inflammation in all cancers at various 2 molecular levels. Gosh. Their group's called the 3 Cancer Genome Analysis, that's working on -- 4 continues to work on ovarian cancer. Sambucetti 5 looks on ovarian cancer with BRCA mutations. 6 Looking -- there are new papers coming out all the 7 time on other risk factors. 8 Q. And if I may ask a very precise question 9 in hopes of moving us along. 10 A. Okay. Sorry. 11 Q. That's fine. 12 A. No worries. 13 Q. Are you aware of any other papers that are 14 works in progress that specifically look at the 15 issue of talc and ovarian cancer? 16 A. I have not read -- 17 MS. O'DELL: Besides the one she 18 mentioned? 19 A. Besides the one I mentioned, I have not 20 read any other data or prepublication drafts. 21 MR. JAMES: Okay. That's all the 22 questions I have for now. 23 MR. KLATT: Oh. 24 THE WITNESS: What are we on? 10s?</p>	<p>1 MR. KLATT: Let me do this. 2 Let's just mark this, the full 3 Asbestos Monograph -- 4 THE WITNESS: Okay. 5 MR. KLATT: -- Doctor, instead of some 6 pages. Let's mark it as the next exhibit. 7 THE COURT REPORTER: It should be 31. 8 (Deposition Exhibit 31 marked for 9 identification.) 10 FURTHER EXAMINATION 11 BY MR. KLATT: 12 Q. Doctor, I'm handing you, and just verify 13 it's what you're looking at. But this -- I'm 14 representing to you this is a copy of the 2012 IARC 15 Asbestos Monograph that's referred to your 16 report and also -- 17 A. Exactly. 18 Q. -- referred to in your testimony multiple 19 times today, correct? 20 A. Correct. 21 Q. And if you would, turn to page 256, 22 please. 23 A. (Complied.) Getting close. 24 Q. Are you at page 256?</p>
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<p>1 14, 13. It may be down here. 11, 10. 2 MR. KLATT: Do you -- I don't -- I'm 3 looking for the IR Asbestos Monograph. 4 THE WITNESS: This is not it? 5 MR. KLATT: No, I don't believe so. 6 THE WITNESS: I mean, it's like -- 7 MS. O'DELL: I don't believe we 8 entered that yet. 9 THE WITNESS: It's got -- this is from 10 the IR Monograph, but it is not the -- 11 MR. KLATT: Do you have the entire 12 monograph -- 13 THE WITNESS: Yes, we do. 14 MR. KLATT: -- in one of those books? 15 THE WITNESS: Yes, we do. 16 MR. KLATT: Can you pull it? 17 THE WITNESS: Second IA. 18 MS. O'DELL: Which monograph? 19 THE WITNESS: The -- 20 MR. KLATT: The 2012 Asbestos 21 Monograph. 22 THE WITNESS: MC. It's the second 23 one. It's not that one. It's the second IA. Yep, 24 that's it.</p>	<p>1 A. I am. 2 Q. Of the IARC 2012 Asbestos Monograph? 3 A. I am. 4 Q. I'm looking in the right-hand column, and 5 I think you looked at this language earlier today. 6 The right-hand column, the middle 7 paragraph says, "The IARC Working Group noted that a 8 causal association between exposure to asbestos and 9 cancer of the ovary was clearly established based on 10 five strongly positive cohort mortality studies of 11 women with heavy occupational exposure to asbestos," 12 correct? 13 A. Correct. 14 Q. And then it cites five studies that you've 15 reviewed, correct? 16 A. Right. 17 Q. None of those studies involve the type of 18 asbestos that's alleged to be in Johnson &amp; Johnson's 19 body powder products, correct? 20 MS. O'DELL: Object to the form. 21 A. I'd have to look at them back to look at 22 the types. I -- I'm sorry. I don't remember the 23 details in these studies -- 24 Q. (BY MR. KLATT) If, in fact --</p>

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<p>1 A. -- at the time.</p> <p>2 Q. -- those five studies involve a type of</p> <p>3 asbestos that hasn't been alleged to be in Johnson &amp;</p> <p>4 Johnson's Baby Powder, then you wouldn't be reliant</p> <p>5 on those, correct?</p> <p>6 MS. O'DELL: Object to the form.</p> <p>7 Misstates the record.</p> <p>8 A. These studies are not about Johnson's Baby</p> <p>9 Powder.</p> <p>10 Q. (BY MR. KLATT) Exactly.</p> <p>11 A. These studies are about asbestos.</p> <p>12 Q. Right. And they're not even done in the</p> <p>13 U.S., are they?</p> <p>14 A. Some of them for sure were in the UK. I</p> <p>15 can look them all up if you want.</p> <p>16 Q. And they were studies of women who had</p> <p>17 heavy occupational exposure to asbestos, correct?</p> <p>18 That's what the IARC Monograph says?</p> <p>19 A. I can -- I can look at that in more detail</p> <p>20 if I find Reid or --</p> <p>21 Q. No, I'm just asking you what the IARC</p> <p>22 Monograph says.</p> <p>23 MS. O'DELL: You're welcome to refer</p> <p>24 to Reid if you'd like.</p>	<p>1 can't remember which studies are that.</p> <p>2 Q. I'm talking about the studies IARC is</p> <p>3 relying on for its conclusion that ovarian cancer --</p> <p>4 A. I'd like to --</p> <p>5 Q. -- is related to --</p> <p>6 THE WITNESS: Get me Reid, will you?</p> <p>7 What is that saying on there?</p> <p>8 Q. (BY MR. KLATT) The studies are cited</p> <p>9 right there, Doctor.</p> <p>10 A. I know. I just --</p> <p>11 MS. O'DELL: She's just reading.</p> <p>12 A. -- was verifying the information before I</p> <p>13 give this to you.</p> <p>14 (Examined exhibit.) Okay. My -- the</p> <p>15 next sentence takes us where we want to go.</p> <p>16 (Paraphrasing.) The conclusion</p> <p>17 received these initial support from studies showing</p> <p>18 women and girls with environmental but not</p> <p>19 occupational exposure. I will give you that now.</p> <p>20 Q. Okay. But it says the link is clearly</p> <p>21 established based on the heavy occupational</p> <p>22 exposure, correct?</p> <p>23 MS. O'DELL: Objection to the form.</p> <p>24 A. That was their initial establishment of</p>
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<p>1 A. I'd like to refer to Reid if I can find</p> <p>2 it, because it's up here as evidence. Early,</p> <p>3 early --</p> <p>4 Q. (BY MR. KLATT) But I'm not asking you</p> <p>5 about Reid. I'm asking you about the IARC</p> <p>6 Monograph.</p> <p>7 A. The Reid includes those studies in a</p> <p>8 meta-analysis and has details on those studies that</p> <p>9 will allow me to refresh my memory --</p> <p>10 Q. All right. I'll withdraw --</p> <p>11 A. -- about them.</p> <p>12 Q. -- the question.</p> <p>13 I want to focus on what IARC's saying</p> <p>14 because you said earlier today you relied on IARC.</p> <p>15 IARC says in Exhibit 31, Doctor --</p> <p>16 IARC says in Exhibit 31 that the link to ovarian</p> <p>17 cancer and asbestos is based on the studies with</p> <p>18 women with heavy occupational exposure, correct?</p> <p>19 That's --</p> <p>20 A. Predominance, it says that. And the</p> <p>21 predominoc- -- the predominant exposure in these</p> <p>22 studies, to my memory, was occupational. But I</p> <p>23 believe some -- some studies were spouses and --</p> <p>24 of people who were nonoccupationally exposed, and I</p>	<p>1 the link.</p> <p>2 Q. (BY MR. KLATT) Now, that very same IARC</p> <p>3 Monograph, turn over to page 280, if you would. It</p> <p>4 says there in the right-hand column about three</p> <p>5 paragraphs down -- do you see where I'm reading?</p> <p>6 A. Yeah.</p> <p>7 Q. This very same IARC Working Group that</p> <p>8 looked at asbestos says, "The association between</p> <p>9 exposure to talc, potential retrograde translocation</p> <p>10 to the ovarian epithelium, and the development of</p> <p>11 ovarian cancer is controversial," correct?</p> <p>12 MS. O'DELL: Objection.</p> <p>13 A. That was their assessment based on</p> <p>14 IARC 2010, which --</p> <p>15 Q. (BY MR. KLATT) And this --</p> <p>16 MS. O'DELL: Excuse me.</p> <p>17 Q. (BY MR. KLATT) I'm sorry. Go ahead.</p> <p>18 A. -- and this volume.</p> <p>19 MS. O'DELL: She was not finished.</p> <p>20 Q. (BY MR. KLATT) And this volume is --</p> <p>21 MS. O'DELL: Excuse me.</p> <p>22 A. And this volume.</p> <p>23 MS. O'DELL: Let her finish, please,</p> <p>24 sir.</p>

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<p style="text-align: right;">Page 358</p> <p>1 Q. (BY MR. KLATT) Are you finished?</p> <p>2 A. I am now.</p> <p>3 MS. O'DELL: She was not finished, and</p> <p>4 it's not gonna be clear on the record.</p> <p>5 Dr. Smith, if you need to finish your</p> <p>6 answer, please go ahead and do that.</p> <p>7 Q. (BY MR. KLATT) I apologize. I thought</p> <p>8 you were finished, and so I didn't mean to interrupt</p> <p>9 you.</p> <p>10 So IARC, on the one hand --</p> <p>11 THE WITNESS: I said it.</p> <p>12 Q. (BY MR. KLATT) -- is saying --</p> <p>13 THE WITNESS: She's got it down.</p> <p>14 MS. O'DELL: Okay.</p> <p>15 Q. (BY MR. KLATT) I'm sorry?</p> <p>16 A. The transcriptionist has what I said.</p> <p>17 This -- 20 -- 93 and 100C, 2010 and 2012.</p> <p>18 Q. Are what IARC cites for stating that the</p> <p>19 association between exposure to talc, potential</p> <p>20 retrograde translocation to the ovarian epithelium,</p> <p>21 and the development of ovarian cancer is</p> <p>22 controversial, correct?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A. That's what they say in probably 2011.</p>	<p style="text-align: right;">Page 360</p> <p>1 facts to substantiate. They are not the same thing,</p> <p>2 so I disagree with their assessment that retrograde</p> <p>3 translocation to the ovarian epithelium is at all</p> <p>4 controversial for any particulate.</p> <p>5 I have talked about the both</p> <p>6 epidemiologic and biochemical by different</p> <p>7 investigators of exposure to talc in vitro and a</p> <p>8 strong epidemiologic history relating talc and</p> <p>9 ovarian cancer.</p> <p>10 So based on what I've been talking</p> <p>11 about for the past 12 hours, I disagree with this.</p> <p>12 Q. (BY MR. KLATT) Okay. Well, that's what I</p> <p>13 wanted to establish.</p> <p>14 On the one hand, when IARC in the</p> <p>15 asbestos monograph in 2012 is talking about exposure</p> <p>16 to talc, translocation to the ovaries, and the</p> <p>17 development of ovarian cancer, they don't say it's</p> <p>18 clearly established at all.</p> <p>19 They -- they, IARC, says it's</p> <p>20 controversial, correct?</p> <p>21 MS. O'DELL: Objection; asked and</p> <p>22 answered.</p> <p>23 A. They're flat wrong.</p> <p>24 Q. (BY MR. KLATT) I'm asking what IARC says.</p>
<p style="text-align: right;">Page 359</p> <p>1 Q. (BY MR. KLATT) So on the one hand,</p> <p>2 they're saying in this monograph that the link to</p> <p>3 ovarian cancer they ascertain is based on every</p> <p>4 occupational exposure, but when they describe the</p> <p>5 association with talc, retrograde translocation to</p> <p>6 the ovaries and ovarian cancer, they don't say it's</p> <p>7 clearly established at all. They say it's</p> <p>8 controversial, correct?</p> <p>9 MS. O'DELL: Object to the form.</p> <p>10 A. I know what they say. I can read their</p> <p>11 words. I would, again, disagree that retrograde</p> <p>12 translocation of particulates to the ovarian</p> <p>13 epithelium is not controversial based on the data</p> <p>14 that I've been talking about for about half the day.</p> <p>15 Q. (BY MR. KLATT) Which IARC also summarizes</p> <p>16 in its 2010 talc monograph and in this monograph?</p> <p>17 A. In 2010 --</p> <p>18 MS. O'DELL: Objection -- excuse me.</p> <p>19 Excuse me.</p> <p>20 Objection. That is -- misstates her</p> <p>21 prior testimony, and you know that.</p> <p>22 So to the degree you understand the --</p> <p>23 the question, Dr. Smith, please go ahead.</p> <p>24 A. I know what they say. I know what I have</p>	<p style="text-align: right;">Page 361</p> <p>1 A. I -- okay. We have read this sentence 14</p> <p>2 times.</p> <p>3 Q. Do you agree with it?</p> <p>4 A. I do not agree with the statement. I</p> <p>5 agree those words are printed on the paper.</p> <p>6 Q. Do you agree that's IARC's position?</p> <p>7 A. IARC printed those things --</p> <p>8 MS. O'DELL: Objection; asked and</p> <p>9 answered.</p> <p>10 A. -- and said that.</p> <p>11 Q. (BY MR. KLATT) Okay. Thank you.</p> <p>12 And they cite their own talc monograph</p> <p>13 in 2010, and they cite their asbestos monograph --</p> <p>14 A. Asked and answered.</p> <p>15 Q. -- and they ask -- you're not the lawyer</p> <p>16 here.</p> <p>17 A. I know it, but I'm getting it.</p> <p>18 Q. IARC, for the statement that the exposure</p> <p>19 to talc translocation to the ovaries and development</p> <p>20 of ovarian cancer is controversial, what IARC</p> <p>21 cites -- listen to me, Doctor -- what IARC cites --</p> <p>22 A. I'm listening. I have my eyes closed, but</p> <p>23 I'm listening.</p> <p>24 Q. -- is their own 2010 talc monograph and</p>

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<p style="text-align: right;">Page 362</p> <p>1 this very 2012 asbestos monograph, correct?</p> <p>2 MS. O'DELL: Excuse me. Asked and</p> <p>3 answered 10 times.</p> <p>4 Q. (BY MR. KLATT) Is that correct?</p> <p>5 MS. O'DELL: Excuse me. Asked and</p> <p>6 answered.</p> <p>7 A. The words are printed on the paper. That</p> <p>8 is what they wrote.</p> <p>9 Q. (BY MR. KLATT) So my statement's correct?</p> <p>10 MS. O'DELL: Objection.</p> <p>11 A. They wrote that, yes.</p> <p>12 Q. (BY MR. KLATT) Not that hard.</p> <p>13 I think we established earlier that</p> <p>14 there's not a single study showing talc applied to</p> <p>15 the external genital area has been shown to migrate</p> <p>16 into the ovaries?</p> <p>17 A. I know of no talc translocation migration</p> <p>18 studies.</p> <p>19 Q. And the Egli study and the Sjösten study</p> <p>20 and the Zervomanoklakis study --</p> <p>21 (Speaking simultaneously.)</p> <p>22 A. I'm not (unintelligible).</p> <p>23 Q. -- that you cited, none of those involve</p> <p>24 talc?</p>	<p style="text-align: right;">Page 364</p> <p>1 Q. (BY MR. KLATT) Okay. Well, let's talk --</p> <p>2 Egli and Zervomanoklakis involved injections of</p> <p>3 particles into something called the vaginal</p> <p>4 posterior fornix, correct?</p> <p>5 A. Um-hum.</p> <p>6 Q. I'm sorry?</p> <p>7 A. Yes.</p> <p>8 Q. And that's not the external genital area,</p> <p>9 is it?</p> <p>10 A. Hum. That is part of the lower genital</p> <p>11 tract.</p> <p>12 Q. The posterior vaginal fornix is the area</p> <p>13 of the vagina right next to the cervix, correct?</p> <p>14 A. Uh-huh.</p> <p>15 Q. So the very top of the vagina, correct?</p> <p>16 A. It's sort of at the very back.</p> <p>17 Q. And so it's not at the external genital</p> <p>18 area, correct?</p> <p>19 A. I didn't say it was external. I said it</p> <p>20 was part of the lower genital tract.</p> <p>21 Q. It's about halfway to the ovaries,</p> <p>22 correct?</p> <p>23 MS. O'DELL: Objection to form.</p> <p>24 A. Yes.</p>
<p style="text-align: right;">Page 363</p> <p>1 A. None of --</p> <p>2 MS. O'DELL: Object to the form.</p> <p>3 A. -- them did.</p> <p>4 Q. (BY MR. KLATT) And they all involve those</p> <p>5 particles being injected into the reproductive</p> <p>6 tract?</p> <p>7 MS. O'DELL: Object to the form.</p> <p>8 A. Absolutely not.</p> <p>9 Q. (BY MR. KLATT) They say poster- --</p> <p>10 A. Sjösten did not inject anything. He had</p> <p>11 corn starch on gloves.</p> <p>12 Q. And was that applied externally or was the</p> <p>13 corn starch --</p> <p>14 A. It's a pelvic examination.</p> <p>15 Q. Let me finish.</p> <p>16 And a pelvic examination involves</p> <p>17 introduction of corn starch on surgical gloves into</p> <p>18 the reproductive tract. It's not specific --</p> <p>19 A. I don't think you'll get any --</p> <p>20 MS. O'DELL: Excuse me. Excuse me.</p> <p>21 Q. (BY MR. KLATT) It's not external</p> <p>22 application, correct?</p> <p>23 MS. O'DELL: Object to the form.</p> <p>24 A. You said "injected."</p>	<p style="text-align: right;">Page 365</p> <p>1 Q. (BY MR. KLATT) And those animals in those</p> <p>2 studies --</p> <p>3 A. They're humans.</p> <p>4 Q. Well, no. You said -- Egli, I thought you</p> <p>5 said was in animals.</p> <p>6 MS. O'DELL: Object to form.</p> <p>7 A. No, Egli's in humans.</p> <p>8 Q. (BY MR. KLATT) Well --</p> <p>9 A. Egli's --</p> <p>10 Q. -- the humans were --</p> <p>11 A. -- in humans.</p> <p>12 Q. The hum- --</p> <p>13 A. Zervomanoklakis is in humans. Sjösten is</p> <p>14 in humans. Hunts is in humans.</p> <p>15 Q. And these humans, then, were given Pitocin</p> <p>16 to stimulate uterine contractions, weren't they?</p> <p>17 A. Some of them in some of the studies.</p> <p>18 Q. Well, that doesn't have anything to do</p> <p>19 with women applying talc externally, does it?</p> <p>20 MS. O'DELL: Object to the form.</p> <p>21 A. No, but it is part of the transport</p> <p>22 mech- -- the contractions of the uterus and the</p> <p>23 fallopian tube are part of the mechanisms of</p> <p>24 transport.</p>

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<p style="text-align: right;">Page 366</p> <p>1 Q. (BY MR. KLATT) And, in fact, in Egli, 2 the -- the study subjects were tilted head down at a 3 15-degree angle, correct? 4 MS. O'DELL: Objection to form. 5 A. Yes. 6 Q. (BY MR. KLATT) And in Sjösten, it was 7 corn starch, not talc, correct? 8 A. Yes. 9 Q. And you said these were a part of 10 gynecologic examinations in which the physician was 11 introducing the corn starch into the reproductive 12 tract, correct? 13 MS. O'DELL: Objection to form. 14 A. On his or her gloves. Not injecting it. 15 Q. (BY MR. KLATT) Health Canada that you've 16 referred to, they just announced a preliminary 17 evaluation and opened it up to public comment, 18 right? 19 A. They are in the 90-day discussion window. 20 Q. And -- well, the discussion window means 21 the public comments can be submitted for the next 90 22 days, correct? 23 A. Correct. 24 Q. And then they have up to two years to make</p>	<p style="text-align: right;">Page 368</p> <p>1 MS. O'DELL: Object to the form. 2 A. Gene expression is part of everything. 3 Q. (BY MR. KLATT) Exactly. It's how we 4 live. 5 If we didn't have gene expression, 6 we'd die, right? 7 A. Right. 8 Q. So the mere fact that they measured gene 9 expression doesn't say anything about causing 10 cancer, does it? 11 A. It's what genes -- 12 MS. O'DELL: Object to the form. 13 A. -- they looked at. 14 Q. (BY MR. KLATT) And Shukla didn't conclude 15 that their findings showed that talc causes 16 ovarian -- 17 MS. O'DELL: Give her a moment to -- 18 Q. (BY MR. KLATT) -- cancer -- 19 MS. O'DELL: -- and just -- 20 Q. (BY MR. KLATT) -- correct? 21 MS. O'DELL: You may look at the study 22 before you answer the question. 23 Q. (BY MR. KLATT) Well, you testified to 24 Shukla study in response to Ms. O'Dell's question</p>
<p style="text-align: right;">Page 367</p> <p>1 a decision whether they're gonna do anything at all 2 or nothing, correct? 3 MS. O'DELL: Object to the form. 4 A. Correct. 5 Q. (BY MR. KLATT) So they haven't made any 6 final conclusions at all, have they? 7 A. They've drawn their conclusions. They 8 will entertain comments. I think their conclusions 9 are compelling. 10 Q. Well, at the end of nine -- at the end of 11 two years, they may decide to do nothing at all 12 based on the evidence they receive, correct? 13 A. It might, but may still be here. 14 Q. The Shukla study that you talked about -- 15 A. Yes. 16 Q. -- that didn't look at any sort of genetic 17 mutations, did it? 18 A. It looked at gene activation. 19 THE WITNESS: Can you get the Shukla? 20 Q. (BY MR. KLATT) Gene expression, correct? 21 A. Gene expression. 22 THE WITNESS: Sorry. Thank you. 23 Q. (BY MR. KLATT) Gene expression is a part 24 of daily living, isn't it?</p>	<p style="text-align: right;">Page 369</p> <p>1 without looking at it. 2 MS. O'DELL: Let me rephrase my 3 objection. 4 If you need to look at a study, you 5 may. If you don't, please feel free to answer Mr. 6 Klatt's questions. 7 Q. (BY MR. KLATT) Doctor, when you were 8 answering Ms. O'Dell's questions about Shukla, you 9 didn't need to look at the study, did you? 10 MS. O'DELL: Objection. 11 A. I want to know -- I want to see the 12 descriptions of -- 13 Q. (BY MR. KLATT) Did they conclude their 14 results of their study showed that talc caused 15 ovarian cancer? 16 A. (Examined exhibit.) So they looked at -- 17 this is the mesothelioma, so we're not -- they 18 looked at subalteration, cell activation, cell 19 motility, immune response, protein metabolic 20 processes, signal transection, changes in 21 extracellular matrix. 22 All of these are pathways looking at 23 MRA levels that are activated in the carcinogenic 24 process in . . .</p>

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<p>1 Q. Doctor, my question is: Shukla nowhere 2 concludes that the results of their experiments 3 showed that talc or even asbestos caused ovarian 4 cancer, correct? 5 A. No, they did not cause ovarian cancer, 6 yes. 7 They upregulated enzymes active in 8 some part of the carcinogenic process. They didn't 9 induce any demonstrated genetic abnormalities. 10 Q. Correct. 11 And if you would turn your attention 12 to page 2000 -- I'm sorry. Page -- do you have a 13 page 121? 14 A. No -- oh, wait. I have a -- this is 15 crazy. I have a 199 and then it goes to 2009 -- oh, 16 wait. That may be the year. 17 Q. I think that's the year. 18 A. Yeah, I think that's the year. 19 Ah. I have a 121, yes. 20 Q. Okay. Do you see a paragraph in the 21 Shukla study on page 121 beginning with, "Several 22 other genes"? 23 A. Yes. 24 Q. "Several other genes uprate -- upregulated</p>	<p>1 A. You can modulate up and you can modulate 2 down. 3 Q. And what they found is that it modulated 4 down, correct? 5 MS. O'DELL: Object to the form. 6 A. I don't see the figure. 7 Q. (BY MR. KLATT) Do you see the next thing 8 they talk about? Upregulation of angiopoietin-4. 9 A. Um-hum. 10 Q. Do you see that? 11 A. Uh-huh. 12 Q. Is thought to play a key role -- or excuse 13 me, play a role in inhibition of tumor cell motility 14 and metastasis. 15 So if you're inhibiting tumor cell 16 motility and metastasis, that's an anticancer 17 property, correct? 18 MS. O'DELL: Objection to the form. 19 A. Yes. 20 Q. (BY MR. KLATT) And then KLF4, 21 Kruppel-like factor 4, is a negative regulator of 22 cell proliferation, correct? 23 A. And can be a positive or negative 24 modulator of DNA transcription.</p>
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<p>1 by talc at 8 hours are affected by asbestos at both 2 8 and 24 hours may be important in repair from 3 mineral-induced responses," correct? 4 A. Correct. 5 MS. O'DELL: Object to the form. 6 Q. (BY MR. KLATT) For example, SOD2 is an 7 antioxidant protein, correct? 8 A. Correct. 9 Q. Antioxidant has anticancer properties, 10 right? 11 MS. O'DELL: Object to the form. 12 A. In general. 13 Q. (BY MR. KLATT) And you see that the next 14 thing they talk about, PTGS2? 15 A. Yes. 16 Q. It's a key enzyme in pros- -- prostanooid 17 bio- -- biosynthesis associated with modulation of 18 mitogenesis and inflammation, correct? 19 MS. O'DELL: Object to the form. 20 A. Correct. 21 Q. (BY MR. KLATT) That's an anticancer 22 property? 23 A. Not necessarily. 24 Q. Well --</p>	<p>1 Q. Well, cancer is uncontrolled cell 2 proliferation, correct? 3 A. You can't -- it can go either way. 4 Q. Well, it says -- 5 MS. O'DELL: Excuse me. She's 6 finished? 7 Q. (BY MR. KLATT) -- it's a negative 8 regulator of cell proliferation. 9 Does it say that? 10 A. Which is different from transcription. It 11 says "positive or negative transcription." 12 Q. But if you're a negative regulator of cell 13 proliferation, that's an anticancer property, 14 correct? 15 MS. O'DELL: Objection to form. 16 A. I think -- 17 MS. O'DELL: She's answered the 18 question. 19 A. -- that's oversimplified. 20 Q. (BY MR. KLATT) What a negative regulator 21 of cell proliferation means it down-regulates 22 self-proliferation, correct? 23 A. Yes. 24 Q. That's anticancer property?</p>

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<p>1 A. I think when you make that big jump, there</p> <p>2 are a whole lot of little steps in there to get to</p> <p>3 that.</p> <p>4 I can't make that conclusion, and I</p> <p>5 don't think you can either.</p> <p>6 Q. I'm just reading what they're saying</p> <p>7 there.</p> <p>8 MS. O'DELL: Object to the form.</p> <p>9 A. No, you're interpreting what they're</p> <p>10 saying because they didn't say it's an anticancer</p> <p>11 drug.</p> <p>12 Q. (BY MR. KLATT) They say it's a negative</p> <p>13 regulator of cell proliferation, correct?</p> <p>14 A. And nowhere in this sentence does it say</p> <p>15 it's anticancer.</p> <p>16 Q. Well, do you want something that increases</p> <p>17 cell proliferation or decreases cell proliferation?</p> <p>18 A. Certainly in repair --</p> <p>19 MS. O'DELL: Objection to form.</p> <p>20 A. -- process. If it's normal epithelium, I</p> <p>21 want -- you don't know enough about this and neither</p> <p>22 do I.</p> <p>23 Can we just keep going?</p> <p>24 Q. (BY MR. KLATT) Sure. That's fine.</p>	<p>1 Q. You're aware that Dr. Saed has just</p> <p>2 started writing about talc in relation to ovarian</p> <p>3 cancer since he's become a retained litigation</p> <p>4 expert by the plaintiffs, right?</p> <p>5 MS. O'DELL: Objection to form.</p> <p>6 A. I can't tell you the exact first time he</p> <p>7 did an experiment or published a result with that.</p> <p>8 I can't -- I . . .</p> <p>9 Q. (BY MR. KLATT) You're not aware of</p> <p>10 Dr. Saed making any sort of connection between talc</p> <p>11 and ovarian cancer before you got involved in this</p> <p>12 litigation, correct?</p> <p>13 A. I -- I'm not aware of that.</p> <p>14 Q. IARC has not said that any of the heavy</p> <p>15 metals you cite in your report increase the risk of</p> <p>16 ovarian cancer, correct?</p> <p>17 A. They have called them Class 1 carcinogens,</p> <p>18 and there's been no association with ovarian cancer</p> <p>19 made in their report.</p> <p>20 Q. And you're not aware of any evidence that</p> <p>21 women who use talc-based body powder products have</p> <p>22 increased blood or tissue levels of cadmium, cobalt,</p> <p>23 chromium, or nickel, compared to women who never use</p> <p>24 those products --</p>
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<p>1 You're not aware of any evidence that</p> <p>2 genital talc use increases vulvar cancer in women --</p> <p>3 A. No.</p> <p>4 Q. -- who use it, correct? Correct?</p> <p>5 A. I said "no." Correct.</p> <p>6 Q. You're not aware of any evidence that</p> <p>7 women who use external genital talc have increased</p> <p>8 risk of vaginal cancer, correct?</p> <p>9 A. I do not.</p> <p>10 Q. And I believe with Mr. --</p> <p>11 A. James.</p> <p>12 Q. -- Mr. Scott James you talked about no --</p> <p>13 awareness of no increase in cervical cancer or</p> <p>14 uterine cancer in talc users, correct?</p> <p>15 A. You are correct.</p> <p>16 Q. And also, talc applied to the external</p> <p>17 genital area would come into contact with the rectal</p> <p>18 area, correct?</p> <p>19 MS. O'DELL: Objection.</p> <p>20 A. It -- yes.</p> <p>21 Q. (BY MR. KLATT) Are you aware of any</p> <p>22 evidence that women who use talc in the genital area</p> <p>23 have an increased risk of rectal cancer?</p> <p>24 A. I do not have any evidence to that effect.</p>	<p>1 A. I know no evidence --</p> <p>2 Q. -- correct --</p> <p>3 MS. O'DELL: Objection; form.</p> <p>4 A. -- to that effect.</p> <p>5 MS. O'DELL: Excuse me. Objection to</p> <p>6 form.</p> <p>7 Q. (BY MR. KLATT) Is that correct?</p> <p>8 A. I know no evidence to that effect.</p> <p>9 Q. And finally, Doctor, and I think it's very</p> <p>10 admirable what you're currently doing with the women</p> <p>11 who are in hospice care for ovarian cancer.</p> <p>12 When you interact with these women,</p> <p>13 you interact not only with the women but with their</p> <p>14 family and friends as well, correct?</p> <p>15 A. Absolutely.</p> <p>16 Q. Now, have you ever told any of their</p> <p>17 family or friends that they shouldn't use talc --</p> <p>18 MS. O'DELL: Objection to form.</p> <p>19 Q. (BY MR. KLATT) -- in the genital area?</p> <p>20 A. I think it would be quite inappropriate to</p> <p>21 have that conversation at that time.</p> <p>22 Q. Well, these are women -- these are</p> <p>23 mothers, sisters, daughters, and female friends of</p> <p>24 these women who are dying with ovarian cancer,</p>

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1	correct?	1	MR. JAMES: Thank you, Dr. Smith.
2	MS. O'DELL: Objection to form.	2	(Discussion off the record.)
3	A. I have never told them -- counseled a	3	THE COURT REPORTER: Leigh, would you
4	family member or a friend or a child of a dying	4	like the witness to read and sign?
5	ovarian cancer patient about genital talc use.	5	MS. O'DELL: Yes, I would.
6	Q. (BY MR. KLATT) You haven't said a word	6	THE COURT REPORTER: Would you like it
7	about it right up until as we sit here today; is	7	to go to you or directly to the witness?
8	that correct?	8	MS. O'DELL: To me.
9	MS. O'DELL: Objection to form.	9	
10	A. Correct.	10	(Deposition concluded at 9:23 p.m.,
11	MR. KLATT: Thank you. That's all I	11	January 9, 2019.)
12	have.	12	
13	MR. JAMES: I don't have any further	13	
14	questions.	14	
15	MS. O'DELL: Okay.	15	
16	FURTHER EXAMINATION	16	
17	BY MS. O'DELL:	17	
18	Q. I have -- have -- let me just ask one	18	
19	question.	19	
20	In the situation when you're	20	
21	counseling a family of a dying patient, would it be	21	
22	inappropriate to have a discussion that Mr. Klatt	22	
23	suggested?	23	
24	A. I feel it would be.	24	

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1	MS. O'DELL: Okay. I have no further	1	CHANGES AND SIGNATURE
2	questions.	2	WITNESS NAME: ELLEN BLAIR SMITH, M.D.
3	FURTHER EXAMINATION	3	DATE: JANUARY 9, 2019
4	BY MR. KLATT:	4	PAGE/LINE CHANGE REASON
5	Q. Well, let me ask one more question about	5	
6	that.	6	
7	Do you ever care for women who are	7	
8	dying from ovarian cancer due to BRCA1 or BRCA2	8	
9	mutations?	9	
10	MS. O'DELL: Object to the form.	10	
11	A. I -- in my life? Yes.	11	
12	Q. (BY MR. KLATT) And you would certainly	12	
13	counsel those women to have their female mothers,	13	
14	sisters, daughters, and friends -- well, mothers,	14	
15	sisters, and daughters tested for those mutations,	15	
16	correct, because you'd want them to take steps to	16	
17	potentially avoid the risk of ovarian cancer.	17	
18	A. Correct.	18	
19	MS. O'DELL: Objection.	19	
20	MR. KLATT: Thank you.	20	
21	MS. O'DELL: I have nothing further.	21	
22	THE VIDEOGRAPHER: This concludes the	22	
23	deposition of Ellen Blair Smith, M.D. Going off the	23	
24	record. The time is 9:22 p.m.	24	

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Ellen Blair Smith, M.D.

<p style="text-align: right;">Page 382</p> <p>1 I, ELLEN BLAIR SMITH, M.D., have read the 2 foregoing deposition and hereby affix my signature 3 that same is true and correct, except as noted 4 above. 5 6 ELLEN BLAIR SMITH, M.D. 7 8 THE STATE OF _____ 9 10 COUNTY OF _____ 11 12 Before me, _____, on 13 this day personally appeared ELLEN BLAIR SMITH, 14 M.D., known to me (or proved to me under oath or 15 through _____) (description of 16 identity card or other document) to be the person 17 whose name is subscribed to the foregoing instrument 18 and acknowledged to me that they executed the same 19 for the purposes and consideration therein 20 expressed. 21 Given under my hand and seal of office 22 this _____ day of _____, 23 2019. 24 _____ NOTARY PUBLIC IN AND FOR THE STATE OF _____</p>	<p style="text-align: right;">Page 384</p> <p>1 following: 2 That the witness, ELLEN BLAIR SMITH, M.D., 3 was duly sworn by the officer and that the 4 transcript of the oral deposition is a true record 5 of the testimony given by the witness; 6 That the original deposition was delivered 7 to SCOTT A. JAMES, custodial attorney; 8 That a copy of this certificate 9 was served on all parties and/or the witness shown 10 herein on _____. 11 I further certify that pursuant to FRCP 12 No. 30(f)(i) that the signature of the deponent was 13 requested by the deponent or a party before the 14 completion of the deposition and the signature is to 15 be returned within 30 days from date of receipt of 16 the transcript. 17 If returned, the attached Changes 18 and Signature Page contains any changes and the 19 reasons therefor. 20 That pursuant to information given to the 21 deposition officer at the time said testimony was 22 taken, the following includes counsel for all 23 parties of record: 24</p>
<p style="text-align: right;">Page 383</p> <p>1 IN THE UNITED STATES DISTRICT COURT 2 FOR THE DISTRICT OF NEW JERSEY 3 4 IN RE: JOHNSON &amp; JOHNSON ) 5 TALCUM POWDER PRODUCTS ) 6 MARKETING, SALES ) 7 PRACTICES, AND PRODUCTS ) MDL NO: 8 LIABILITY LITIGATION ) 16-2738 (FLW)(LHG) 9 ) 10 THIS DOCUMENT RELATES TO ) 11 ALL CASES ) 12 13 14 15 16 17 18 19 20 21 22 23 24</p> <p style="text-align: center;">REPORTER'S CERTIFICATE</p> <p>----- DEPOSITION OF ELLEN BLAIR SMITH, M.D. TAKEN JANUARY 9, 2019 -----</p> <p>I, Karen L. D. Schoeve, Registered Diplomate Reporter, Certified Realtime Reporter, and Realtime Systems Administrator, residing in the State of Texas, do hereby certify that the foregoing proceedings were reported by me and that the foregoing transcript constitutes a full, true, and correct transcription of my stenographic notes, to the best of my ability and hereby certify to the</p>	<p style="text-align: right;">Page 385</p> <p>1 FOR PLAINTIFFS' STEERING COMMITTEE: 2 P. LEIGH O'DELL, ESQUIRE 3 DR. MARGARET M. THOMPSON, ESQUIRE 4 BEASLEY ALLEN, P.C. 5 218 Commerce Street 6 P.O. Box 4160 7 Montgomery, Alabama 36104 8 T: 334.269.2343 (Ms. O'Dell) 9 F: 334.954.7555 (Ms. O'Dell) 10 C: 512.695.1708 (Ms. Thompson) 11 T: 800.898.2034 (Ms. Thompson) 12 F: 855.674.1818 (Ms. Thompson) 13 leigh.odell@beasleyallen.com 14 margaret.thompson@beasleyallen.com 15 --AND-- 16 CYNTHIA L. GARBER, ESQUIRE 17 ROBINSON CALCAGNIE, INC. 18 19 Corporate Plaza Drive 19 Newport Beach, California 92660 20 C: 949.456.0037 21 T: 949.720.1288 22 F: 949.720.1292 23 cgarber@robinsonfirm.com 24 --AND-- PAULA R. BROWN, ESQUIRE BLOOD HURST &amp; O'REARDON, LLP 501 West Broadway, Suite 1490 San Diego, California 92101 T: 619.338.1100 F: 619.338.1101 pbrown@bholaw.com  (Continued on following page)</p>

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# Exhibit 145

1 UNITED STATES DISTRICT COURT  
2 DISTRICT OF NEW JERSEY  
3  
4 -----x  
5 IN RE JOHNSON & JOHNSON ) MDL No.  
6 TALCUM POWDER PRODUCTS ) 16-2738 (FLW)(LHG)  
7 MARKETING SALES PRACTICES, )  
8 AND PRODUCTS LIABILITY )  
9 LITIGATION )  
10 )  
11 THIS DOCUMENT RELATES TO )  
12 ALL CASES )  
13 -----x

14  
15  
16  
17 VIDEOTAPED DEPOSITION OF  
18 JACK SIEMIATYCKI, Ph.D.  
19  
20 MONTREAL, CANADA  
21  
22 THURSDAY, JANUARY 31, 2019  
23  
24  
25 9:49 A.M.

25 Reported by: Leslie A. Todd

<p style="text-align: right;">Page 2</p> <p>1 Deposition of JACK SIEMIATYCKI, Ph.D., held at 2 the offices of: 3 4 5 CHUM Research Center 6 Montreal, Canada 7 8 9 10 11 12 Pursuant to notice, before Leslie Anne Todd, 13 Court Reporter and Notary Public in and for the 14 District of Columbia, who officiated in 15 administering the oath to the witness. 16 17 18 19 20 21 22 23 24 25</p>	<p style="text-align: right;">Page 4</p> <p>1 APPEARANCES (Continued): 2 3 RICHARD GOLOMB, ESQUIRE 4 GOLOMB &amp; HONIK, LLP 5 1835 Market Street 6 Suite 2900 7 Philadelphia, Pennsylvania 19103 8 (215) 278-4449 9 rgolomb@golombhonik.com 10 ON BEHALF OF THE JOHNSON &amp; JOHNSON DEFENDANTS: 11 KIMBERLY OLVEY BRANSCOME, ESQUIRE 12 KIRKLAND &amp; ELLIS LLP 13 333 South Hope Street 14 Los Angeles, California 90071 15 (213) 680-8370 16 kimberly.branscome@kirkland.com 17 JESSICA BRENNAN, ESQUIRE 18 DRINKER BIDDLE &amp; REATH LLP 19 600 Campus Drive 20 Florham Park, New Jersey 07932 21 (973) 540-1000 22 jessica.brennan@dbr.com 23 24 25</p>
<p style="text-align: right;">Page 3</p> <p>1 A P P E A R A N C E S 2 3 ON BEHALF OF THE PLAINTIFFS: 4 CHRISTOPHER V. TISI, ESQUIRE 5 LEVIN PAPANTONIO, LLP 6 316 South Baylen Street 7 Pensacola, Florida 32502 8 (850) 435-7184 9 ctisi@levinlaw.com 10 MICHELLE A. PARFITT, ESQUIRE 11 ASHCRAFT &amp; GEREL, LLP 12 4900 Seminary Road, Suite 650 13 Alexandria, Virginia 22311 14 (703) 997-1774 15 MParfitt@ashcraftlaw.com 16 ALASTAIR J.M. FINDEIS, ESQUIRE 17 NAPOLI SHKOLNIK, PLLC 18 360 Lexington Avenue 19 11th Floor 20 New York, New York 10017 21 (212) 397-1000 22 23 24 25</p>	<p style="text-align: right;">Page 5</p> <p>1 APPEARANCES (Continued): 2 3 ON BEHALF OF THE PCPC: 4 RENEE APPEL, ESQUIRE (Telephonically) 5 SEYFARTH SHAW LLP 6 975 F Street, N.W. 7 Washington, DC 20004 8 (202) 828-5371 9 rappel@seyfarth.com 10 ON BEHALF OF THE IMERY'S DEFENDANTS: 11 MICHAEL R. KLATT, ESQUIRE 12 GORDON &amp; REES SCULLY MANSUKHANI, LLP 13 816 Congress Avenue, Suite 1510 14 Austin, Texas 78701 15 (512) 391-0183 16 mklatt@grsm.com 17 ON BEHALF OF PTI: 18 CAROLINE M. TINSLEY, ESQUIRE (for PTI) 19 TUCKER ELLIS, LLP 20 100 South 4th Street, Suite 600 21 St. Louis, Missouri 63102 22 (314) 571-4965 23 caroline.tinsley@tuckerellis.com 24 ALSO PRESENT: 25 FABIO DEFELICE (Videographer)</p>

Jack Siemiatycki, Ph.D.

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<p style="text-align: right;">Page 7</p> <p>1           E X H I B I T S (Continued)</p> <p>2           (Attached to transcript)</p> <p>3 SIEMIATYCKI DEPOSITION EXHIBITS               PAGE</p> <p>4 No. 7   JS EpiTech Inc. bill for</p> <p>5       Professional Services, August 9 -</p> <p>6       November 16, 2018               46</p> <p>7 No. 8   JS EpiTech Inc. bill for</p> <p>8       Professional Services, July 1 -</p> <p>9       August 2, 2018                   48</p> <p>10 No. 9   Report of Jack Siemiatycki dated</p> <p>11       October 4th, 2016 (not attached)   58</p> <p>12 No. 10   Expert Report of Jack Siemiatycki</p> <p>13       Msc, PhDn Talcum Powder Use and</p> <p>14       Ovarian Cancer (not attached)     61</p> <p>15 No. 11   Expert Report of Jack Siemiatycki</p> <p>16       MSc, PhD on Talcum Powder Use and</p> <p>17       Ovarian Cancer (with handwritten</p> <p>18       notations)                       110</p> <p>19 No. 12   Berge 2012 report (not attached)   194</p> <p>20 No. 13   Schildkraut report (not attached)   214</p> <p>21 No. 14   Anita Koushik information from</p> <p>22       Environepi website               278</p> <p>23 No. 15   Pages from Environepi website</p> <p>24       discussing Group Research Topics   285</p> <p>25</p>	<p style="text-align: right;">Page 9</p> <p>1           P R O C E E D I N G S</p> <p>2           -----</p> <p>3           THE VIDEOGRAPHER: Good morning. We're</p> <p>4 now on the record. My name is Fabio DeFelice.</p> <p>5 I'm the videographer for Golkow Litigation</p> <p>6 Services. Today's date is January 31st of 2019.</p> <p>7 The time is 9:49 a.m.</p> <p>8           This video deposition is being held at</p> <p>9 the CHUM Research Center in Montreal, Canada, in</p> <p>10 the matter In Re: Johnson &amp; Johnson Talcum Powder</p> <p>11 Products in the United States District Court for</p> <p>12 the Eastern District of New Jersey. The case</p> <p>13 number is 16-2738.</p> <p>14           The deponent is Jack Siemiatycki, Ph.D.</p> <p>15           The counsel will be noted on the</p> <p>16 stenographic record. The court reporter is Leslie</p> <p>17 Todd, and will now swear in the witness.</p> <p>18           JACK SIEMIATYCKI, Ph.D.,</p> <p>19           and having been first duly sworn,</p> <p>20           was examined and testified as follows:</p> <p>21           D I R E C T   E X A M I N A T I O N</p> <p>22 BY MS. BRANSCOME:</p> <p>23       Q   Good morning, Dr. Siemiatycki.</p> <p>24       A   Good morning. Nice to meet you.</p> <p>25       Q   We met just before the deposition</p>

<p>Page 10</p> <p>1 started, but my name is Kimberly Branscome, and I</p> <p>2 am here to ask you questions today on behalf of</p> <p>3 Johnson &amp; Johnson.</p> <p>4 Is that all right?</p> <p>5 A Thank you. Yes.</p> <p>6 Q All right. We are taking your</p> <p>7 deposition today in the case of In Re: Johnson &amp;</p> <p>8 Johnson Talc Litigation, MDL.</p> <p>9 Is it your understanding that you have</p> <p>10 been designated as a testifying expert in that</p> <p>11 case?</p> <p>12 A Yes.</p> <p>13 Q When were you first contacted about</p> <p>14 serving as an expert witness in the MDL</p> <p>15 litigation?</p> <p>16 A I believe it was in the spring or summer</p> <p>17 of 2018, but I'm not positive about that.</p> <p>18 Q Who contacted you?</p> <p>19 A Ms. Parfitt.</p> <p>20 Q Have you communicated with any other</p> <p>21 lawyers regarding your work on the talc MDL?</p> <p>22 A I've had a couple of meetings with</p> <p>23 Ms. Parfitt and her colleagues that she works</p> <p>24 with.</p> <p>25 Q Can you identify the individuals with</p>	<p>Page 12</p> <p>1 anyone else present at those meetings?</p> <p>2 A No.</p> <p>3 Q You didn't have anyone from your team,</p> <p>4 for example, present?</p> <p>5 A No.</p> <p>6 MS. PARFITT: Objection. Form.</p> <p>7 BY MS. BRANSCOME:</p> <p>8 Q What did you do to prepare for your</p> <p>9 deposition today?</p> <p>10 A Do you mean from the beginning of my</p> <p>11 involvement in the MDL case back last summer or do</p> <p>12 you mean just in the last few days?</p> <p>13 Q Let's take it more broadly.</p> <p>14 What have you done to develop your</p> <p>15 opinions in this case, and then specifically to</p> <p>16 prepare for your deposition?</p> <p>17 A I reviewed -- I rereviewed the</p> <p>18 literature about talc and ovarian cancer,</p> <p>19 scientific literature. I evaluated it, I wrote a</p> <p>20 report about it. And in the last few days, I went</p> <p>21 over all of the -- not all, but a lot of the</p> <p>22 material that I had gone through initially and</p> <p>23 just clarified for myself, looked for any issues</p> <p>24 that I had missed the first time around, things</p> <p>25 like that.</p>
<p>Page 11</p> <p>1 whom you have met in addition to Ms. Parfitt?</p> <p>2 A Yes, there are two, and they are here</p> <p>3 present. Chris Tisi and Alastair --</p> <p>4 MR. FINDEIS: Findeis.</p> <p>5 THE WITNESS: Say that again.</p> <p>6 MS. PARFITT: Findeis.</p> <p>7 THE WITNESS: And that's -- thank you.</p> <p>8 BY MS. BRANSCOME:</p> <p>9 Q How many meetings have you had to</p> <p>10 prepare for your expert opinions in the MDL?</p> <p>11 A One yesterday and one about a month --</p> <p>12 about three weeks ago.</p> <p>13 Q Where did those meetings take place?</p> <p>14 A Here.</p> <p>15 Q And by "here," do you mean in Montreal?</p> <p>16 A In Montreal, yes.</p> <p>17 Q How long did each meeting last?</p> <p>18 A Yesterday's was about four, five hours</p> <p>19 maybe. Four or five hours. And the earlier one,</p> <p>20 I guess all told, about ten hours maybe.</p> <p>21 Q Did the ten-hour meeting take place over</p> <p>22 one day?</p> <p>23 A Over two days.</p> <p>24 Q In addition to the attorneys that you</p> <p>25 just identified for the record and yourself, was</p>	<p>Page 13</p> <p>1 Q As part of your review of materials in</p> <p>2 preparation for today, did you identify anything</p> <p>3 in your review that changed the opinions that you</p> <p>4 have offered in the expert report in the MDL?</p> <p>5 A No. Those opinions remain valid.</p> <p>6 Q When you say that you rereviewed the</p> <p>7 scientific literature in preparation for the</p> <p>8 development of your opinions in the MDL, what did</p> <p>9 you mean by "rereviewed"?</p> <p>10 A Well, I had reviewed -- I've reviewed</p> <p>11 evidence around talc and ovarian cancer on a few</p> <p>12 different occasions. The first time was in 2006</p> <p>13 when I was on an international review committee on</p> <p>14 the topic. Then in 2015, '16, '17, in preparation</p> <p>15 for another litigation regarding talc and ovarian</p> <p>16 cancer. Then in the summer/fall of 2018, in</p> <p>17 preparation for writing a report that was</p> <p>18 submitted for this case. And then in the last</p> <p>19 week or two, roughly speaking, I went over all of</p> <p>20 that. So I refer to that as a rereview.</p> <p>21 Q Have you ever discussed your deposition</p> <p>22 with any of -- of the other experts designated by</p> <p>23 the plaintiffs in the MDL?</p> <p>24 A No, I haven't.</p> <p>25 Q Have you discussed your expert opinions</p>

<p style="text-align: right;">Page 14</p> <p>1 with any of the other experts designated by the 2 plaintiffs in the MDL? 3 A No, I haven't. 4 Q Are you aware of the list of experts 5 that have been designated by the plaintiffs in the 6 MDL? 7 A I'm aware of at least some of them. I'm 8 not sure if I'm aware of all of them, but I'm 9 aware of some of them. 10 Q Who specifically are you aware of? 11 A Singh, McTiernan, Laura Plunkett. And 12 there are a few more, and I could look it up. 13 Q I'd like to start by just marking the 14 deposition notice for your deposition as 15 Exhibit 1. 16 Dr. Siemiatycki, you will see two large 17 binders over there in front of you. This will be 18 tab 1. 19 So I'd like -- 20 A I see it. 21 Q I'd like to mark for identification 22 the document behind tab 1, which is 23 Dr. Siemiatycki's deposition notice as Exhibit 1 24 to this deposition. 25 MS. PARFITT: Do you want to give me --</p>	<p style="text-align: right;">Page 16</p> <p>1 your deposition that were submitted by plaintiffs' 2 counsel in the MDL. And this one we actually will 3 need to mark a copy, because it's not in your 4 binder. 5 (Exhibit No. 2 was marked for 6 identification.) 7 MS. BRANSCOME: Do you have an extra 8 copy, Michelle? 9 MS. PARFITT: I do. Not a worry. I got 10 it. 11 BY MS. BRANSCOME: 12 Q Dr. Siemiatycki, have you ever seen the 13 document that has been marked as Exhibit 2, which 14 is the plaintiffs' general objections to your 15 deposition notice? 16 A I'm not sure. 17 MS. PARFITT: I will represent for the 18 record that's not been provided to 19 Dr. Siemiatycki. 20 BY MS. BRANSCOME: 21 Q All right. So if you could, 22 Dr. Siemiatycki, did you bring any materials with 23 you today to the deposition? 24 A Yes, I brought a lot of documents, just 25 in case.</p>
<p style="text-align: right;">Page 15</p> <p>1 Do you want me to just mark them? Will 2 that help you, instead of reaching across the 3 table? It's up to you. I can put the stickers on 4 it. 5 (A discussion was held off the record.) 6 (Exhibit No. 1 was marked for 7 identification.) 8 BY MS. BRANSCOME: 9 Q Dr. Siemiatycki, are you familiar with 10 the document that we have just marked as 11 deposition Exhibit 1? 12 A I've seen something like this. I'm -- 13 not reading through it, I'm not sure if it's 14 exactly the same document that I have seen before, 15 but I guess this is kind of the standard format of 16 notice that is sent to experts ahead of time. So 17 I've seen -- I've seen that. 18 Q Do you understand that what has been 19 marked as Exhibit 1, which is the notice for your 20 deposition, requests that you bring certain 21 documents with you to this deposition? 22 A Yes. 23 Q All right. And just for completeness 24 and at the request of plaintiffs' counsel, I will 25 also mark as Exhibit 2 the general objections to</p>	<p style="text-align: right;">Page 17</p> <p>1 Q Can you identify for me, and we can 2 start with a general category first, if that's 3 helpful, the materials that you brought with you 4 today to your deposition? 5 A Well, I brought my report. I brought an 6 addendum to my report, which I think has been 7 provided to you. 8 MS. PARFITT: Yes, that was the table. 9 THE WITNESS: It's a long -- it's a set 10 of -- 11 MS. PARFITT: I have a copy of that if 12 you wish to have it marked. Do you want it -- if 13 you give me a number, I will put it on this one. 14 BY MS. BRANSCOME: 15 Q Let's see. Yeah, let's go ahead and 16 mark the addendum to your expert report as 17 Exhibit 3. 18 (Exhibit No. 3 was marked for 19 identification.) 20 BY MS. BRANSCOME: 21 Q Dr. Siemiatycki, could you just confirm 22 for the record that what we have marked as 23 Exhibit 3 is in fact the complete addendum to your 24 MDL expert report? 25 A I -- I believe it is. I believe it is.</p>

<p style="text-align: right;">Page 18</p> <p>1 Q What else did you bring with you today?</p> <p>2 A I'm not sure if this is the right time</p> <p>3 to mention it, but there were a couple of -- in</p> <p>4 the past few days I picked up a couple of typos in</p> <p>5 my report, and I've hand scribbled them on my</p> <p>6 copy, and I can tell you about those very quickly,</p> <p>7 but I'm not sure if this is now the right time for</p> <p>8 this or later.</p> <p>9 Q I will ask you about any corrections</p> <p>10 that you have, but it is good to know that the</p> <p>11 report you brought with you has some handwriting</p> <p>12 on it, so we will make sure to mark that copy.</p> <p>13 A Okay.</p> <p>14 Q What else did you bring with you today?</p> <p>15 A I brought -- well, I brought three</p> <p>16 binders of material that were part of the -- the</p> <p>17 references to my report.</p> <p>18 MS. PARFITT: And if I may, I provided</p> <p>19 counsel in advance of the deposition a thumb drive</p> <p>20 that contains all of Dr. Siemiatycki's report but</p> <p>21 also the references related to that report.</p> <p>22 THE WITNESS: I brought a couple of</p> <p>23 binders -- well, more than a couple. It looks</p> <p>24 like five binders of different documents that I</p> <p>25 thought might be useful in answering questions</p>	<p style="text-align: right;">Page 20</p> <p>1 Agency for Research on Cancer, of the meeting held</p> <p>2 in Lyon in 2006. The book was published in 2010,</p> <p>3 and it contains an evaluation of talc</p> <p>4 carcinogenicity as of 2006.</p> <p>5 The next one is a textbook of</p> <p>6 epidemiology that is probably considered the most</p> <p>7 respected one in the field at this point, authored</p> <p>8 by Rothman, T -- R-O-T-H-M-A-N, Greenland,</p> <p>9 G-R-E-E-N-L-A-N-D, and Lash, L-A-S-H.</p> <p>10 MR. KLATT: Dr. Siemiatycki, is there a</p> <p>11 particular edition or is there --</p> <p>12 THE WITNESS: Oh, yeah. Yeah, this one</p> <p>13 is third edition. Thank you.</p> <p>14 The fourth one is kind of a handbook</p> <p>15 called Dictionary of Epidemiology, edited by</p> <p>16 Porta, P-O-R-T-A, which is kind of a very basic</p> <p>17 book of definitions.</p> <p>18 And the fifth one is called An</p> <p>19 Introduction to Meta-Analysis. The first author</p> <p>20 is Borenstein, B-O-R-E-N-S-T-E-I-N.</p> <p>21 BY MS. BRANSCOME:</p> <p>22 Q All right. Focusing first on the books</p> <p>23 that you brought with you, why did you bring with</p> <p>24 you a book about Risk Factors --</p> <p>25 A For cancer.</p>
<p style="text-align: right;">Page 19</p> <p>1 that you might ask. So it was -- I was just</p> <p>2 speculating on the types of questions you might</p> <p>3 ask and brought documents that might help to</p> <p>4 answer or to support arguments or statements that</p> <p>5 I would make. I brought five --</p> <p>6 MS. PARFITT: You can get --</p> <p>7 THE WITNESS: -- which --</p> <p>8 MS. PARFITT: -- the texts --</p> <p>9 THE WITNESS: The textbooks. I brought</p> <p>10 five books with me, again in the same spirit that</p> <p>11 things might come up that it would be helpful to</p> <p>12 refer to material in these books. One -- should I</p> <p>13 tell you what they are?</p> <p>14 BY MS. BRANSCOME:</p> <p>15 Q If you would, please, identify each of</p> <p>16 the books --</p> <p>17 A Okay.</p> <p>18 Q -- for the record, and we will return to</p> <p>19 the eight binders that you just mentioned.</p> <p>20 A One is a book called Risk Factors for</p> <p>21 Cancer in the Workplace. And it's a book that I</p> <p>22 wrote 30 years ago about occupational causes of</p> <p>23 cancer.</p> <p>24 The other one -- the next one is the</p> <p>25 monograph of IARC, which is the International</p>	<p style="text-align: right;">Page 21</p> <p>1 Q -- for Cancer in the Workplace?</p> <p>2 A Because it has -- in that book I -- I</p> <p>3 described my research. I described the research</p> <p>4 findings from my projects in this area. I also</p> <p>5 described the process of conducting epidemiologic</p> <p>6 research and drawing inferences from epidemiologic</p> <p>7 data, and how -- what are the considerations that</p> <p>8 would be used in drawing inferences from</p> <p>9 epidemiologic data for cancer causation. And I</p> <p>10 thought this might come up during the day.</p> <p>11 Q Do the methodological principles that</p> <p>12 you outline in your book, Risk Factors for Cancer</p> <p>13 in the Workplace, are those still current in your</p> <p>14 view today?</p> <p>15 A Yes.</p> <p>16 Q And why specifically did you want to</p> <p>17 have this book available to you during your</p> <p>18 deposition?</p> <p>19 A In case any of the statements that I've</p> <p>20 made in my report about evaluating causation and</p> <p>21 how epidemiology is used for evaluating causation</p> <p>22 are challenged. And specifically, I was</p> <p>23 anticipating that there may be challenges to the</p> <p>24 fact that my approach to this question might be</p> <p>25 new and just sort of concocted in the context of</p>

<p style="text-align: right;">Page 22</p> <p>1 the litigation, and I wanted to show that in my 2 own sort of intellectual history, these ideas have 3 been there forever but certainly for the last 30 4 years, and that these are commonly held views. 5 Q Are there specific chapters within the 6 book that you brought with you that you would 7 direct someone to to gain information about the 8 methodology that you applied in the MDL? 9 MS. PARFITT: Objection. Form. 10 THE WITNESS: I'm sorry. Could you 11 repeat the question? 12 BY MS. BRANSCOME: 13 Q Understanding that what you brought with 14 you -- 15 A Yes. 16 Q -- is a complete book -- 17 A Yes. 18 Q -- are there specific chapters that you 19 contend contain an explanation of the methodology 20 that is similar to what you have applied in your 21 analysis in the MDL? 22 MS. PARFITT: Objection. Form, broad. 23 THE WITNESS: So I would say there are 24 two chapters that have relevance to the issue at 25 hand. The last chapter contains a discussion of</p>	<p style="text-align: right;">Page 24</p> <p>1 A Yeah. 2 Q -- in the MDL? 3 A I -- yes, I -- I collected as much 4 information, data from different research studies 5 as possible. I evaluated those studies. I 6 ordered them according to the types of evidence 7 that they provide. I tried to synthesize the 8 evidence in particular in the basket of 9 epidemiologic research on the topic. And I 10 juxtaposed the information from epidemiologic 11 evidence with evidence derived from other domains 12 which are provided by other experts. And I made a 13 professional judgment about how all of that fits 14 with different ways of understanding the 15 relationship between perennial use of talc and the 16 risk of ovarian cancer. 17 Q Is the methodology that you just 18 described that you used in forming your opinions 19 in the MDL described in the textbook that you 20 brought with you about risk factors in the 21 workplace? 22 A It is implicit. It is implicit in the 23 work of epidemiologists, and it's implicit in the 24 way we synthesize information. So, in 25 epidemiologic practice, the role of -- there's no</p>
<p style="text-align: right;">Page 23</p> <p>1 causality and how to use epidemiology in the 2 process of determining causality. 3 The first -- the second chapter contains 4 information -- excuse me, I think it's the second 5 chapter -- contains information about different 6 epidemiologic research designs, and it's a 7 discussion of case-controlled studies, cohort 8 studies, and other types of epidemiologic designs 9 and their relative advantages and disadvantages. 10 BY MS. BRANSCOME: 11 Q Is there a description of the 12 methodology that you have applied in your analysis 13 in the MDL that is directly described in the book 14 that you just referenced? 15 MS. PARFITT: Objection. Form. 16 THE WITNESS: I'm not sure what you mean 17 by "directly," and I'm not sure what you mean by 18 "methodology." 19 BY MS. BRANSCOME: 20 Q Did you apply a specific methodology in 21 reaching your opinions here in the MDL? 22 A What do you mean by "a specific 23 methodology"? 24 Q Did you -- did you use a methodology in 25 forming your opinions --</p>	<p style="text-align: right;">Page 25</p> <p>1 cookbook recipe in how you start the day and 2 finish the day. You collect data. You use your 3 best judgment about how to synthesize and 4 integrate it. And I guess it comes under the 5 rubric of weight of evidence. You look at all of 6 the evidence, and you (weigh it according to your 7 professional judgment. 8 And most of the agencies that have any 9 policies or statements about synthesizing 10 information will talk about collecting 11 information, evaluating it, weighing it, and 12 making a judgment about it. 13 Q If someone were reviewing just your 14 report in the MDL, would they be able to replicate 15 the weight that you gave different pieces of 16 evidence that you considered? 17 A The synthesis of scientific information 18 is not an automated process. It can't be done by 19 a robot. And in every description of how such 20 evidence is synthesized and integrated, the final 21 step always involves professional judgment, and as 22 it should, because there are too many moving parts 23 in all of this to be able to, a priori, set up an 24 algorithm that allows you to automate and arrive 25 at some score that tells you, yes or no, this</p>

<p style="text-align: right;">Page 26</p> <p>1 agent is dangerous or not dangerous or something 2 like that.</p> <p>3 So in line with everything I've done in 4 my career, everything that I've been involved with 5 in international and national agencies, whether 6 it's USNCI or the World Health Organization or 7 other agencies, the process depends critically on 8 judgment of the people who are making the 9 decisions or who are making the evaluations.</p> <p>10 Q Respectfully, Dr. Siemiatycki, that was 11 not my question.</p> <p>12 My question was, could someone by 13 reviewing the report that you have provided in the 14 MDL replicate your analysis in the sense that they 15 would understand the weight that you gave to each 16 piece of evidence you considered?</p> <p>17 A I think to a considerable extent I've 18 given fairly explicit information in the report on 19 all of the components of information that I used 20 and the relative weight, but -- not in a 21 quantitative way, but the relative importance that 22 I attribute to different parts of the evidence 23 package.</p> <p>24 Q You did not do any type of scoring 25 system, for example, in considering the various</p>	<p style="text-align: right;">Page 28</p> <p>1 selected, when they were selected, when they were 2 followed up, how -- all of these things may have a 3 different score, and you may have a hundred 4 dimensions to evaluate on each study. And nobody 5 has come up with a -- a usable, useful, 6 replicatable method for integrating all of this.</p> <p>7 There have been some attempts and there are some 8 scoring systems out there. The fact that there 9 are scoring -- that someone has published a 10 scoring system, and that even a committee has, 11 does not mean that it's valid.</p> <p>12 But I -- my professional opinion, and 13 that of I think many other people -- because 14 typically studies are not scored in this way.</p> <p>15 That's -- when people review evidence. Or if 16 they -- anyway, typically they are not, and my 17 feeling is that there is no valid way really of 18 doing it.</p> <p>19 But the -- in order to sort of complete 20 the answer to I think what's behind your question 21 of why I didn't do such a thing in my report with 22 all of the studies is that I adopted early on -- I 23 made a decision early on to avoid excluding 24 studies from my analysis based on my opinion about 25 the quality of the study. This is a decision that</p>
<p style="text-align: right;">Page 27</p> <p>1 underlying studies that you evaluated. Is that 2 fair?</p> <p>3 A No -- no, I did not, because I don't 4 consider that a valid procedure.</p> <p>5 Q Why is that not a valid procedure?</p> <p>6 A Because I don't think epidemiologic 7 studies can be summarized in single-digit scores. 8 There are too many different aspects of a study, 9 and any attempt to do so, I think is flawed and --</p> <p>10 Q Why is the attempt to assigning a score, 11 single digit or otherwise, a flawed methodology?</p> <p>12 A Because there are so many -- a study can 13 be good in one dimension, mediocre in a third, 14 excellent in a fourth, bad in a fifth, so-so in a 15 sixth, and so on.</p> <p>16 There are so many dimensions of a study, 17 and each one of them can be rated. And that's -- 18 that is something that I do do. I evaluate 19 everything from participation rate to the 20 population in which the study was carried out, to 21 the way the questions were asked in the 22 questionnaire, to the way the information from the 23 questionnaire was -- was coded and categorized, to 24 the way the design of the -- whether its case 25 controlled or otherwise, how the subjects were</p>	<p style="text-align: right;">Page 29</p> <p>1 other meta-analyses have also made implicitly. I 2 don't know if they've made it explicitly, but 3 there are no studies that have -- as far as I 4 know, there are no meta-analyses that have 5 literally excluded studies on the basis of quality 6 or -- or done a systematic attempt to do this.</p> <p>7 And I made a decision early on that if I 8 tried to -- if I went down the road of eliminating 9 some studies from my analysis, this would be 10 criticized as some form of cherry-picking, and in 11 an attempt to avoid that criticism, I decided I 12 would include all pieces of evidence, 13 notwithstanding my opinion of the overall quality 14 of the study.</p> <p>15 Q Okay. Dr. Siemiatycki, that was a very 16 long answer, but I will try to unpack a few --</p> <p>17 A Yes.</p> <p>18 Q -- portions of that.</p> <p>19 So you would agree that in order for a 20 methodology to be valid, it has to be a process 21 that can be replicated?</p> <p>22 MS. PARFITT: Objection. Form.</p> <p>23 THE WITNESS: What do you mean by 24 "replicated"? You mean that someone else 25 following exactly the same steps and the -- making</p>

<p style="text-align: right;">Page 30</p> <p>1 the same assumptions as the -- the person who did                  2 the analysis would be able to end up with the same                  3 statistical estimates at the end? Is that what                  4 you mean? Or do you mean that they would make the                  5 same judgments?                  6 BY MS. BRANSCOME:                  7 Q Well, Dr. Siemiatycki, you indicated one                  8 of the reasons why you don't agree with using a                  9 quantitative point system was that a methodology                  10 had not been developed that was, I believe you                  11 said, useful, usable and replicable.                  12 What did you mean by the word                  13 "replicable" when you used it in your own answer?                  14 A Did I use the word "replicable" in that                  15 sentence? Can I -- can I read that? (Peruses                  16 monitor.)                  17 I'm not sure what I had in mind with the                  18 use -- the word -- yes, you can produce a                  19 replicable system, but it doesn't mean that it's                  20 valid. So useful and usable, yes. I don't think                  21 that there is one that would capture, for                  22 observational epidemiology, the -- all of the                  23 components that are necessary really to tease out                  24 good and/or bad studies.                  25 BY MS. BRANSCOME:</p>	<p style="text-align: right;">Page 32</p> <p>1 giving to the pieces of evidence that he or she is                  2 considering in reaching their ultimate conclusion.                  3 Is that fair?                  4 MS. PARFITT: Objection. Form.                  5 THE WITNESS: It depends what you mean                  6 by "weight." If you mean by "weight" a                  7 quantitative number, then, no, that's not                  8 necessary.                  9 If you mean sort of a heuristic,                  10 qualitative understanding of the relative                  11 importance of different components of evidence,                  12 then I would say yes. It's important to know what                  13 played into a -- a reviewer's opinion.                  14 BY MS. BRANSCOME:                  15 Q You also indicated that you do in fact                  16 rate studies. What did you mean by that?                  17 A Sorry. Can we read back where I said                  18 that? I -- (peruses monitor.)                  19 I haven't found it, but I -- I think I                  20 meant it as a synonym for evaluate. I think I                  21 meant I evaluate different studies.                  22 Q Okay. If I could direct your                  23 attention --                  24 A Yes.                  25 Q -- to pages -- page 19, lines 6</p>
<p style="text-align: right;">Page 31</p> <p>1 Q My question to you, though,                  2 Dr. Siemiatycki, is that, is it important for a                  3 methodology to be replicable?                  4 A It is important -- the most important is                  5 for it to be valid. The replicability is an issue                  6 that involves judgment. Different scientists may                  7 have different judgments about the value of                  8 different components of evidence. That diversity                  9 of judgment is not a bad thing, and there's no                  10 benefit to science in forcing everyone to have the                  11 same judgment within some scoring system.                  12 So science progresses from collection of                  13 data and from different scientists evaluating the                  14 data, and from the same information base different                  15 scientists can make different judgments about it,                  16 and in that sense, the final evaluations are not                  17 necessarily replicable because different                  18 scientists can make different judgments.                  19 But they are understandable. You need                  20 the different processes to be sufficiently                  21 understandable that different readers and so on of                  22 reports can understand how you came to the                  23 conclusions.                  24 Q And so it is important to be able to                  25 understand what weight a particular scientist is</p>	<p style="text-align: right;">Page 33</p> <p>1 through 8.                  2 A Of -- 19 of -- of what?                  3 Q Of the transcript that's --                  4 A Okay.                  5 Q -- in front of you, which understanding                  6 is just a rough, but if you want to review your                  7 answer.                  8 A Sure. (Peruses document.)                  9 Yes, here by "rated," I meant evaluated.                  10 Q Did you rank the different pieces of                  11 evidence that you considered in forming your                  12 opinion with respect to talc and the risk of                  13 ovarian cancer?                  14 A I -- I've never done that in the                  15 hundreds and hundreds of evaluations I've carried                  16 out, nor in this one do I actually put a score on                  17 different components of -- of a study. Yeah.                  18 Q My question is slightly different,                  19 Dr. Siemiatycki.                  20 It's ranking them relative to each                  21 other. So whether or not you're assigning a                  22 specific quantitative number to the study, do you                  23 evaluate this is, for instance, the most important                  24 study and this is the least important study on a                  25 particular topic?</p>

<p style="text-align: right;">Page 34</p> <p>1 MS. PARFITT: Objection. Form.</p> <p>2 THE WITNESS: You mean overall or in --</p> <p>3 in each dimension that the -- that a study is</p> <p>4 comprised of?</p> <p>5 BY MS. BRANSCOME:</p> <p>6 Q Did you do any type of ranking of that</p> <p>7 nature, be it in a subtopic or overall?</p> <p>8 A Not -- not explicitly, no.</p> <p>9 Q You mentioned at the -- at the end of</p> <p>10 your answer that you made a decision not to</p> <p>11 exclude studies because you would not want to face</p> <p>12 the criticism of cherry-picking; is that correct?</p> <p>13 A Yes, I said that.</p> <p>14 Q What is your understanding of the</p> <p>15 criticism of cherry-picking?</p> <p>16 A My understanding is that one would --</p> <p>17 one might look at a body of evidence, have a</p> <p>18 preconceived notion about the topic, the</p> <p>19 hypothesis under consideration, and use those</p> <p>20 studies that support that hypothesis and discard</p> <p>21 the other ones in some way.</p> <p>22 Q Is that good science, in your opinion?</p> <p>23 A No, that's not good science.</p> <p>24 Q Why not?</p> <p>25 A Because it doesn't produce an objective</p>	<p style="text-align: right;">Page 36</p> <p>1 conclusion.</p> <p>2 BY MS. BRANSCOME:</p> <p>3 Q When I asked you the question of whether</p> <p>4 or not the methodology you applied here in forming</p> <p>5 your opinion in the MDL is contained in the book</p> <p>6 that you wrote about Risk Factors for Cancer in</p> <p>7 the Workplace, you said it was implicit.</p> <p>8 Is that methodology explicitly described</p> <p>9 in that textbook or any of the other textbooks you</p> <p>10 brought with you today?</p> <p>11 A I'm not sure that the methodology -- you</p> <p>12 know, I think it -- the collection of data, the</p> <p>13 evaluation of data, the judgment about the</p> <p>14 collection of data is a part of the scientific</p> <p>15 method, and it is so engrained and implicit in</p> <p>16 epidemiology and in other sciences that you don't</p> <p>17 really need to -- and scientists don't write in</p> <p>18 their books or in their -- unless they're talking</p> <p>19 to first-year students -- talk about this. It's</p> <p>20 so elementary that those aspects are not really</p> <p>21 described. One goes further in describing</p> <p>22 specific methodologies that would pertain to the</p> <p>23 topic under consideration.</p> <p>24 Q Are there different ways to perform a</p> <p>25 meta-analysis?</p>
<p style="text-align: right;">Page 35</p> <p>1 portrait of reality.</p> <p>2 Q If a scientist were to selectively</p> <p>3 identify studies that were supportive of his or</p> <p>4 her preconceived notion, would you consider that</p> <p>5 analysis to be a valid one?</p> <p>6 MS. PARFITT: Objection. Form.</p> <p>7 THE WITNESS: Do you mean -- just -- I'm</p> <p>8 just trying to parse your question. You said if a</p> <p>9 scientist were to identify studies that were</p> <p>10 supportive, et cetera, but also that were in</p> <p>11 opposition or to exclude ones that are in</p> <p>12 opposition?</p> <p>13 BY MS. BRANSCOME:</p> <p>14 Q Fair enough.</p> <p>15 So referring back to the scenario that</p> <p>16 you have described as cherry- picking --</p> <p>17 A Yes.</p> <p>18 Q -- if a scientist were to engage in</p> <p>19 cherry-picking, would you consider the ultimate</p> <p>20 conclusion that that scientist reached with</p> <p>21 respect to causation or increased risk of an agent</p> <p>22 to be a valid one?</p> <p>23 A It should be suspect --</p> <p>24 MS. PARFITT: Objection. Form.</p> <p>25 THE WITNESS: It would be a suspect</p>	<p style="text-align: right;">Page 37</p> <p>1 A Yes.</p> <p>2 Q Okay. Did the method that you chose in</p> <p>3 developing your meta-analysis, is that explicitly</p> <p>4 described in any of the materials you either</p> <p>5 brought here with you today or of which you are</p> <p>6 aware in the scientific community?</p> <p>7 A So it partly depends what you mean by "a</p> <p>8 meta-analysis." And in my lexicon, meta-analysis</p> <p>9 is a statistical procedure for summarizing a body</p> <p>10 of -- a set of results from individual studies.</p> <p>11 And that procedure is pretty standard -- has been</p> <p>12 pretty standard since the 1980s and 1990s, and</p> <p>13 there are some refinements since then.</p> <p>14 Sorry, I may have lost the thread of</p> <p>15 your question.</p> <p>16 Q If I were to try to look at a piece of</p> <p>17 scientific literature, be it in a book or an</p> <p>18 article, to find a published description of the</p> <p>19 method that you used to perform your meta-analysis</p> <p>20 in the MDL, where would I look?</p> <p>21 A The meta-analysis was conducted using a</p> <p>22 software that is well known, that is commercially</p> <p>23 available, and I think everyone would recognize</p> <p>24 the validity of the statistical procedures under</p> <p>25 those -- under that.</p>

<p style="text-align: right;">Page 38</p> <p>1 If you're asking about which -- you 2 know, there are decisions to be made about which 3 studies to include, about which results from 4 studies to include, and all of that sort of thing, 5 which is not strictly part of the statistics of 6 meta-analysis, it's sort of the step before 7 meta-analysis, and that part is utterly unique to 8 each situation.</p> <p>9 So if you're doing a meta-analysis of 10 clinical trials that have all been designed 11 basically in an identical way for an 12 antihypertensive medication, and whether the study 13 is done in Australia or California or Canada, the 14 design is pretty standard, and a lot of it can 15 be -- you can -- and you end up basically with a 16 single result from the study, what is the impact 17 on blood pressure -- the average impact on blood 18 pressure among people who use it who were given 19 the drug, the experimental group versus a 20 comparison group, et cetera, that is one type of 21 preparation for a meta-analysis.</p> <p>22 If you're dealing with observational 23 epidemiology, as we are in the case of ovarian 24 cancer, and some of the particularities of the 25 literature in this domain, there are a lot of</p>	<p style="text-align: right;">Page 40</p> <p>1 clarify.</p> <p>2 So the three -- the three binders that 3 you referred to as sort of this first set of 4 materials, are those all references that are 5 identified specifically in your report from the 6 MDL?</p> <p>7 A Yes, I believe so. And just to be 8 clear, when I was sent this material from the 9 lawyers' office, it arrived in four binders. I'm 10 not sure if you received the same four binders. I 11 have re- -- I've taken some things out of there, 12 so I have three binders of those things. Just -- 13 I don't know if there's confusion just between the 14 three and four, but...</p> <p>15 Q What did you remove from the set of 16 materials that you were provided by plaintiffs' 17 counsel?</p> <p>18 A I removed the IARC reports, which I have 19 in books, so I didn't need to carry around 20 hundreds and hundreds of pages extra.</p> <p>21 I removed some other -- there was 22 another report with, you know, thousands of -- 23 hundreds or -- at least of pages where I thought 24 the relevant material was in -- contained in about 25 20 pages. So I kept -- in material that I carry</p>
<p style="text-align: right;">Page 39</p> <p>1 decisions that need to be made in the run-up to 2 the meta-analysis.</p> <p>3 Q So in the situation where you are 4 dealing with observational epidemiology, would it 5 be fair to say that you are applying unique 6 judgment in the selection of the studies that you 7 include in your meta-analysis and, more 8 specifically, what data from those studies you 9 include.</p> <p>10 MS. PARFITT: Objection. Form.</p> <p>11 THE WITNESS: Any meta-analysis in this 12 area would absolutely need to apply professional 13 judgments to those things.</p> <p>14 BY MS. BRANSCOME:</p> <p>15 Q Okay.</p> <p>16 A Mine included and every -- everyone 17 else's included.</p> <p>18 Q All right. So, Dr. Siemiatycki, getting 19 back to the materials that you brought with you 20 today, you mentioned that you brought three 21 binders of scientific literature. Was that 22 correct?</p> <p>23 A Three binders of the references to my 24 report.</p> <p>25 Q Okay. So that's what I wanted to</p>	<p style="text-align: right;">Page 41</p> <p>1 around, I kept the 20 pages and put the rest away 2 in a box.</p> <p>3 Q Do you remember which document that was?</p> <p>4 A If you give me a minute, I'll try to 5 recreate that.</p> <p>6 Q We can check that at the break if you 7 want --</p> <p>8 A Yeah. Sure, sure.</p> <p>9 Q -- to identify that document.</p> <p>10 So then you -- you spoke about an 11 additional five binders --</p> <p>12 A Yeah.</p> <p>13 Q -- that you brought with you that 14 contain documents that might help you answer 15 questions during the deposition.</p> <p>16 Can you describe the contents of those 17 five binders. I'm trying to avoid marking all of 18 these as exhibits.</p> <p>19 A Yeah. Please.</p> <p>20 Okay. Let me just reach down and look 21 at their covers.</p> <p>22 Yeah, so one contains the recent 23 manuscript of a study by Taher, et al., a Canadian 24 meta-analysis of the issue, plus -- let me see if 25 there's anything else in there. I -- I think</p>

<p style="text-align: right;">Page 42</p> <p>1 that's it. It's such a -- such a big report with  2 all the appendices and so on, that it takes up a  3 whole binder.  4 Another one, a smaller one, contains the  5 meta -- the main meta-analyses that have been done  6 in this area, apart from the Taher one. So the  7 Berge, Penninkilampi, a few other older ones,  8 Langseth and some of the older ones.  9 Q Are those materials that are in the set  10 of meta-analysis, the second binder, if you will,  11 are they replicated also in the other set of three  12 binders that you brought with you?  13 A Yes, they are.  14 Q Okay.  15 A Yes, they are.  16 Sorry. There's -- there's another one  17 in -- like that which contains all of the original  18 epidemiology studies that I used or that were  19 available to be used in the meta-analysis. And I  20 had this binder in my previous -- in the previous  21 case that I testified on, and I thought I -- I'd  22 like to have one binder here just of the  23 epidemiology studies because the thick binders,  24 it's harder for me to find articles, so it would  25 be easier for me to find them in this binder. So</p>	<p style="text-align: right;">Page 44</p> <p>1 identification.)  2 BY MS. BRANSCOME:  3 Q Now, Dr. Siemiatycki, with the exception  4 of a copy of your report, which you previously  5 testified has some handwritten annotations on it,  6 do any of the other materials that you brought  7 with you today have any notes, handwritten or  8 typed, or highlighting or any other form of  9 annotation?  10 A Yes. The -- the epidemiology studies  11 and probably the meta-analyses, the previous  12 meta-analyses. I -- I tend to scribble notes when  13 I'm reading an article on the side, so some of  14 those may very well have scribbled notes on -- in  15 the margins or things underlined.  16 Q Dealing first with the binder of the  17 original epidemiological studies that you said you  18 had at a prior deposition, have you annotated that  19 in any way since you brought that to another  20 deposition?  21 A Since today? Sorry.  22 MS. BRANSCOME: Michelle, perhaps you  23 could help me.  24 MS. PARFITT: Sure. Yeah, absolutely.  25 MS. BRANSCOME: Has that specific binder</p>
<p style="text-align: right;">Page 43</p> <p>1 all of these are in the big binders.  2 And there's another one with Health  3 Canada weight of evidence guidelines. Also  4 guidelines from a European agency on weight of  5 evidence and evaluation. I think there might be  6 something from FDA about that, and also some of  7 the information regarding agency -- what agencies  8 have put on their websites, if anything, about  9 talc, which would include the National Cancer  10 Institute and some other agencies.  11 So these are mainly -- well, partly  12 printouts from websites. Partly the Canadian Risk  13 Management scope for talc published very recently  14 from the Canadian Department of Health. And this  15 sort of information. Not -- not all of those are  16 in the thick binders.  17 Q Are all of the documents in the binder  18 that you are holding there, which I think is your  19 fifth binder, are all of those documents  20 identified within your report or in your reference  21 materials?  22 A No.  23 Q I would like to mark that binder as  24 Exhibit 4.  25 (Exhibit No. 4 was marked for</p>	<p style="text-align: right;">Page 45</p> <p>1 been marked as an exhibit at a prior deposition?  2 MS. PARFITT: Let me see which one.  3 Ms. Branscome, I don't want to  4 represent -- and I would tell you that these were  5 all the studies that he's had over the course of  6 the last few years. I can't imagine it wasn't  7 asked for in prior depositions, but I can't -- I  8 can't represent --  9 MS. BRANSCOME: Okay.  10 MS. PARFITT: -- one way or another. I  11 really can't.  12 MS. BRANSCOME: Let's go ahead. I would  13 like to mark the binder --  14 MS. PARFITT: I will tell you this --  15 maybe I can. There are pink numbers, number 10,  16 number 14, which suggest to me that they might  17 have been referenced in a deposition at one point  18 in time as an exhibit.  19 THE WITNESS: Not -- some of them, but  20 not all of them, have those numbers.  21 MS. PARFITT: Okay.  22 THE WITNESS: They also have numbers in  23 the corner of my -- my team's personal filing  24 system of articles, so things like that.  25 MS. BRANSCOME: Out of an abundance of</p>

<p style="text-align: right;">Page 46</p> <p>1 caution, we will mark the binder that has been 2 described as containing the original 3 epidemiological studies as Exhibit 5, and the 4 binder that contains the meta-analyses as 5 Exhibit 6. 6 (Exhibit Nos. 5 and 6 were marked 7 for identification.) 8 BY MS. BRANSCOME: 9 Q Did you bring anything else with you to 10 the deposition today? 11 A Cell phone, glasses, et cetera, but no. 12 Q I was provided before the deposition 13 began with a single piece of paper that I 14 understand to be a bill for professional services. 15 If we could mark a copy of that as 16 Exhibit 7. 17 MS. BRANSCOME: Michelle, I don't know 18 if you have an extra copy. 19 MS. PARFITT: I do. 20 (Exhibit No. 7 was marked for 21 identification.) 22 MS. PARFITT: I have additional copies 23 for counsel, if you would like. 24 MS. BRANSCOME: I think we passed one 25 around.</p>	<p style="text-align: right;">Page 48</p> <p>1 A Okay. 2 Q So why don't we mark as Exhibit 8 the 3 bill for professional services that covers the 4 month of July. 5 (Exhibit No. 8 was marked for 6 identification.) 7 MS. PARFITT: Sure. I don't have extras 8 of those. Does anyone have a clamp? If I could 9 have one of those? Thank you. 10 MR. TISI: Number 7, for the record, is 11 the one that goes to November. 12 MS. BRANSCOME: We'll -- we'll clear it 13 up. 14 MR. TISI: Thank you. 15 THE WITNESS: Got it. 16 BY MS. BRANSCOME: 17 Q So, Dr. Siemiatycki, you have two 18 exhibits in front of you there, an Exhibit 7 and 19 an Exhibit 8. 20 Do they both contain bills for 21 professional services for the work that you have 22 done in connection with this litigation? 23 A Yes, they do. 24 Q And what has been marked as Exhibit 7 25 covers a work period of August 9th through</p>
<p style="text-align: right;">Page 47</p> <p>1 BY MS. BRANSCOME: 2 Q Dr. Siemiatycki, do you recognize the 3 document that's been placed in front of you that's 4 been marked as Exhibit 7? 5 A Yes, I do. 6 Q And could you describe for the record 7 what this document is. 8 A It's a bill for services that I sent to 9 Ms. Parfitt dated November 18, 2018, in which I 10 billed for work done between August and November 11 2018 on the MDL case. 12 Q Is it correct that this is a bill that 13 covers 56 hours that you billed in connection with 14 your work on this case in the month of July 15 through August 2nd, 2018? 16 A Sorry, do -- July? Is this the same -- 17 MS. PARFITT: August. I have August to 18 November. 19 THE WITNESS: Do you have a bill labeled 20 July? 21 MS. PARFITT: We have July to August, 22 and here's the August -- 23 BY MS. BRANSCOME: 24 Q Sorry, we had different pieces of paper, 25 Dr. Siemiatycki.</p>	<p style="text-align: right;">Page 49</p> <p>1 November 16th, 2018, during which you billed 136 2 hours; is that correct? 3 A That's correct. 4 Q And then Exhibit 8 covers the period of 5 time July 1st through August 2nd, 2018, over which 6 you billed 56 hours; is that correct? 7 A That's correct. 8 Q And you bill for your time at \$450 an 9 hour, correct? 10 A That's correct. 11 Q Do the two bills for professional 12 services that have been marked as Exhibits 7 and 8 13 contain any time for work done by others at your 14 direction? 15 A They contain work that has been done by 16 a couple of -- by one research assistant, and I 17 make an arrangement with her to reimburse her for 18 her time. So it's -- it's covered in these, yes. 19 Q Okay. And so how is your research 20 assistant's time billed to plaintiffs' counsel? 21 A It's not billed. I -- I adjust the 22 billable hours to reflect the time that she works 23 for me. 24 Q So if I was looking at Exhibit 7 and 25 Exhibit 8, how much in terms of hours of this</p>

<p style="text-align: right;">Page 50</p> <p>1 reflects your personal time?</p> <p>2 A Between 95 percent and 98 percent,</p> <p>3 almost all of it.</p> <p>4 Q And do the two exhibits that you have in</p> <p>5 front of you there, Exhibit 7 and Exhibit 8, does</p> <p>6 that cover all of the work that you have done in</p> <p>7 connection with forming your opinions in this</p> <p>8 case, meaning the MDL?</p> <p>9 A In forming the opinions for the report,</p> <p>10 yes.</p> <p>11 Q These bills do not include time that you</p> <p>12 spent preparing for today's deposition, correct?</p> <p>13 A That's correct.</p> <p>14 Q About how much time have you spent</p> <p>15 preparing for today's deposition?</p> <p>16 A I would say the time since November 18,</p> <p>17 which is referenced here, to today, there were</p> <p>18 actually two components. One was preparing for</p> <p>19 the deposition. Another was a bit of a flurry of</p> <p>20 activity in December, I think it was, when a</p> <p>21 couple of reports from Health Canada and from</p> <p>22 the Taher group were published, and I reviewed and</p> <p>23 tried to think about that information as well.</p> <p>24 So just to be as precise as possible, I</p> <p>25 just want to make that clear. It's not -- it</p>	<p style="text-align: right;">Page 52</p> <p>1 paper and the Health Canada statement?</p> <p>2 A No, I didn't.</p> <p>3 Q Did you annotate any of the materials</p> <p>4 that you reviewed?</p> <p>5 A I'm -- I'm not sure. I typically have a</p> <p>6 pen in my hand when I'm reading, so I couldn't say</p> <p>7 that I never underlined anything or -- I just</p> <p>8 don't recall making any -- and I don't know that I</p> <p>9 could find -- if I did look at it in December, I'm</p> <p>10 not sure I could find that copy because I -- I</p> <p>11 tend to print things over when -- and I -- there</p> <p>12 was nothing written that I wanted to retain. I</p> <p>13 didn't write anything that I have used or -- yeah.</p> <p>14 MS. BRANSCOME: We've been going for a</p> <p>15 little over an hour. Is now a good time to take a</p> <p>16 break?</p> <p>17 THE WITNESS: It's a great time.</p> <p>18 THE VIDEOGRAPHER: We are going off the</p> <p>19 record at 10:55 a.m.</p> <p>20 (Recess.)</p> <p>21 THE VIDEOGRAPHER: This begins disc</p> <p>22 number 2 in the deposition of Jack Siemiatycki.</p> <p>23 We're going back on the record at 11:15 a.m.</p> <p>24 BY MS. BRANSCOME:</p> <p>25 Q Before we took the break,</p>
<p style="text-align: right;">Page 51</p> <p>1 wasn't only preparation. But I -- I guess we're</p> <p>2 talking about a couple of weeks' work in -- since</p> <p>3 November, but between six and ten days maybe,</p> <p>4 something in that ballpark.</p> <p>5 Q And how would -- what would that be in</p> <p>6 terms of hours?</p> <p>7 A Between 40 and 60 hours or -- subject to</p> <p>8 revision, I could -- I could look that up.</p> <p>9 Q Have you billed plaintiffs' counsel for</p> <p>10 that time yet?</p> <p>11 A No, I haven't.</p> <p>12 Q Presumably you will be billing them for</p> <p>13 the time you spend here today during your</p> <p>14 deposition as well, correct?</p> <p>15 A I -- I presume so as well.</p> <p>16 Q You referenced a flurry of activity in</p> <p>17 December related to the Health Canada information</p> <p>18 becoming public.</p> <p>19 Did you produce or generate any type of</p> <p>20 written work product in connection with your</p> <p>21 review of those materials?</p> <p>22 A No, I didn't.</p> <p>23 Q Did you take any notes while reviewing</p> <p>24 the materials that came out in December -- around</p> <p>25 December 2018 related to the Taher manuscript and</p>	<p style="text-align: right;">Page 53</p> <p>1 Dr. Siemiatycki, we were looking at the two bills</p> <p>2 for professional services that have been marked as</p> <p>3 Exhibit 7 and Exhibit 8.</p> <p>4 And so in addition to the 56 hours that</p> <p>5 are on Exhibit 8, the 136 hours on Exhibit 7, and</p> <p>6 the approximately 40 to 60 hours you have spent</p> <p>7 since mid-November of 2018, how much time have you</p> <p>8 spent in connection with your opinions across all</p> <p>9 talc litigation?</p> <p>10 MS. PARFITT: Objection to form.</p> <p>11 THE WITNESS: Including the previous</p> <p>12 case that I was involved in, you're saying?</p> <p>13 BY MS. BRANSCOME:</p> <p>14 Q Yes.</p> <p>15 A Whew. I -- four to six weeks maybe</p> <p>16 or -- I spent, I think, nearly two weeks in LA</p> <p>17 while that case was going on, so that's one big</p> <p>18 block of time. And then I -- at least a month</p> <p>19 full time, the equivalent of, before that. But,</p> <p>20 I'm sorry, I can't be more precise.</p> <p>21 Q What would that be in terms of hours?</p> <p>22 A Hours. Let's say eight hours a day --</p> <p>23 30, 40 -- 400 hours plus or minus 200.</p> <p>24 Q So a range of between 200 to 600 hours,</p> <p>25 do you think?</p>

<p style="text-align: right;">Page 54</p> <p>1 MS. PARFITT: Object.</p> <p>2 THE WITNESS: It would be more than 200</p> <p>3 for sure. So -- to the best of my recollection,</p> <p>4 it might be between 400 and 600. But...</p> <p>5 BY MS. BRANSCOME:</p> <p>6 Q How much have you billed to date for all</p> <p>7 of the work you've done in connection with talc</p> <p>8 litigation?</p> <p>9 A Well, I -- I don't remember.</p> <p>10 MS. PARFITT: Don't guess.</p> <p>11 THE WITNESS: I don't remember a total.</p> <p>12 BY MS. BRANSCOME:</p> <p>13 Q Do you charge \$450 per hour for all</p> <p>14 types of work that you have done in connection</p> <p>15 with the talc litigation?</p> <p>16 A Yes, I do.</p> <p>17 Q Do the fees that you charge in</p> <p>18 connection with your work as an expert witness in</p> <p>19 the talc litigation go directly to you personally?</p> <p>20 A Yes, they do. Well, they go to a</p> <p>21 corporation that -- that I control, as you see in</p> <p>22 the bills.</p> <p>23 Q Do you pay anyone else for the -- using</p> <p>24 the funds that the corporation has received for</p> <p>25 the expert work you've done in connection with the</p>	<p style="text-align: right;">Page 56</p> <p>1 do you currently spend performing work in</p> <p>2 connection with litigation?</p> <p>3 A By presently, can you give me a time</p> <p>4 frame? You don't mean today, I presume. When you</p> <p>5 say -- do you mean in the last year? In the last</p> <p>6 10 years?</p> <p>7 Q Let's say over -- over the past 12</p> <p>8 months, what percent of your professional time was</p> <p>9 spent performing work in connection with</p> <p>10 litigation?</p> <p>11 A Ten to 20 percent ballpark.</p> <p>12 Q And has that percentage of time spent on</p> <p>13 work in connection with litigation changed over</p> <p>14 the past five years, for example?</p> <p>15 A Yes, it's very variable depending on</p> <p>16 requests for participation in litigation. So in</p> <p>17 the past five years, my main contact with</p> <p>18 litigation has been in the ovarian cancer cases,</p> <p>19 but at -- around five years ago, I was also</p> <p>20 working on two other cases in Canada.</p> <p>21 Sorry, what was the question?</p> <p>22 Q Sure. How -- I'll ask a new one.</p> <p>23 How has the percentage of time that --</p> <p>24 A Oh, oh.</p> <p>25 Q -- you spend in connection with work</p>
<p style="text-align: right;">Page 55</p> <p>1 talc litigation?</p> <p>2 MS. PARFITT: Objection. Form.</p> <p>3 THE WITNESS: Yes, when I ask someone to</p> <p>4 do some specific tasks, I pay them for that.</p> <p>5 BY MS. BRANSCOME:</p> <p>6 Q And are the fees that you pay to other</p> <p>7 individuals for tasks that they do in support of</p> <p>8 your work, do those fees get billed to plaintiffs'</p> <p>9 counsel?</p> <p>10 A No, they don't.</p> <p>11 Q Can you give me an approximation of how</p> <p>12 much you have paid to others from the fees you</p> <p>13 have billed to plaintiffs' counsel?</p> <p>14 A In MDL or in total?</p> <p>15 Q In all of the talc litigation.</p> <p>16 A My guesstimate would be that it's in the</p> <p>17 order of 2 or 3 or 4 percent -- maybe 2 percent of</p> <p>18 the total that I've billed.</p> <p>19 Q So it's fair to say that approximately</p> <p>20 96 to 98 percent of all the fees that have been</p> <p>21 billed to plaintiffs' counsel for your work as an</p> <p>22 expert in the talc litigation will come to you</p> <p>23 personally?</p> <p>24 A Yes.</p> <p>25 Q What percent of your professional time</p>	<p style="text-align: right;">Page 57</p> <p>1 done related to litigation changed?</p> <p>2 A Any litigation, right?</p> <p>3 Q Yes.</p> <p>4 A Or -- or talc litigation?</p> <p>5 Q I'll start with all litigation.</p> <p>6 A So it's -- as I said, it's very variable</p> <p>7 from month to month. And -- and -- I mean, I</p> <p>8 guess over the past five years, it has kind of</p> <p>9 averaged out at about 10 percent of my time, 10 to</p> <p>10 20 percent of my time.</p> <p>11 Q And over the past two years, has all of</p> <p>12 the litigation work you've been doing, has that</p> <p>13 been exclusively focused on talc?</p> <p>14 A Yes.</p> <p>15 Q The report that -- sorry, the report you</p> <p>16 prepared in connection with the MDL is not the</p> <p>17 first expert report you have generated with</p> <p>18 respect to a potential link between talc and</p> <p>19 ovarian cancer, correct?</p> <p>20 A That's correct.</p> <p>21 Q You produced a report in connection with</p> <p>22 the talcum powder litigation dated October 4th,</p> <p>23 2016, correct?</p> <p>24 A That's correct.</p> <p>25 Q If you could turn in your binder there</p>

<p style="text-align: right;">Page 58</p> <p>1 to tab 2.</p> <p>2 A In this big binder?</p> <p>3 Q Yes, please.</p> <p>4 Is the document behind tab 2 your expert</p> <p>5 report dated October 4th, 2016, that related to</p> <p>6 the talcum powder litigation?</p> <p>7 A Yes, it is.</p> <p>8 MS. BRANSCOME: I would like to mark</p> <p>9 that as Exhibit 9.</p> <p>10 (Exhibit No. 9 was marked for</p> <p>11 identification.)</p> <p>12 BY MS. BRANSCOME:</p> <p>13 Q The report marked as Exhibit 9 was not</p> <p>14 drafted for a particular case; is that correct?</p> <p>15 A I -- I -- I'd have to defer -- I'm not</p> <p>16 exactly sure sometimes whether these reports refer</p> <p>17 to a specific case or not.</p> <p>18 Q Okay. Let me do it this way: What was</p> <p>19 the question that you were attempting to answer in</p> <p>20 the report that has been marked as Exhibit 9?</p> <p>21 A So the question was the generic question</p> <p>22 of whether there is a causal relationship between</p> <p>23 use of talcum powder products and ovarian cancer.</p> <p>24 Q And specifically, the report marked as</p> <p>25 Exhibit 9, were you looking specifically at</p>	<p style="text-align: right;">Page 60</p> <p>1 specific to the Echeverria case, correct?</p> <p>2 A Correct.</p> <p>3 Q So the expert report that described the</p> <p>4 opinions that you were offering in that case is</p> <p>5 the one that we have just marked as Exhibit 9. Is</p> <p>6 that fair?</p> <p>7 MS. PARFITT: Objection. Form.</p> <p>8 THE WITNESS: I -- I'm -- I'm hesitating</p> <p>9 because I'm not sure what the significance of the</p> <p>10 phrase "the expert report that you offered" is. I</p> <p>11 didn't -- I didn't in a sense offer this report</p> <p>12 for -- at that trial. I testified at that trial,</p> <p>13 and they had this expert report available to them.</p> <p>14 BY MS. BRANSCOME:</p> <p>15 Q Okay. Let me ask it this way: You</p> <p>16 generated an expert report specific to the MDL,</p> <p>17 correct?</p> <p>18 A Yes.</p> <p>19 Q And we are going to look at that --</p> <p>20 A Yes.</p> <p>21 Q -- but that is a report that is dated at</p> <p>22 some point in 2018, correct?</p> <p>23 A Correct.</p> <p>24 Q Did you generate an expert report at any</p> <p>25 time in between the expert report that you</p>
<p style="text-align: right;">Page 59</p> <p>1 perineal or genital use of talc?</p> <p>2 A That was the focus, yes.</p> <p>3 Q Did your 2016 report address any cancer</p> <p>4 risk associated with the inhalation of talc?</p> <p>5 A Not that I recall. It certainly wasn't</p> <p>6 a focus. There may have been some reason to</p> <p>7 allude to that issue, but I can't recall that</p> <p>8 it -- that there was.</p> <p>9 Q Okay. You had your deposition taken on</p> <p>10 December 15th and 16th, 2016, correct?</p> <p>11 A I believe so.</p> <p>12 Q And that deposition was for two specific</p> <p>13 cases, the Oules and the Daniels case, correct?</p> <p>14 A I guess so. But again, I -- that --</p> <p>15 I'm -- I don't recall exactly which cases.</p> <p>16 Q You also have testified at trial in a</p> <p>17 case involving allegations about Johnson's Baby</p> <p>18 Powder, correct?</p> <p>19 A That's correct.</p> <p>20 Q And that was the Echeverria case?</p> <p>21 A Yes, it was.</p> <p>22 Q And you testified in trial in August of</p> <p>23 2017, correct?</p> <p>24 A Correct.</p> <p>25 Q You did not issue an expert report</p>	<p style="text-align: right;">Page 61</p> <p>1 generated there in October 2016 and the expert</p> <p>2 report you have supplied that's dated November</p> <p>3 2018?</p> <p>4 A No, I did not.</p> <p>5 Q All right. So if I may, I would like to</p> <p>6 actually mark your copy of your 2018 report. And</p> <p>7 that will be marked as Exhibit 10, if you have</p> <p>8 that in front of you.</p> <p>9 (Exhibit No. 10 was marked for</p> <p>10 identification.)</p> <p>11 (Counsel conferring.)</p> <p>12 BY MS. BRANSCOME:</p> <p>13 Q To be clear, for the record, I'm marking</p> <p>14 as Exhibit 10 your MDL expert report, but it is</p> <p>15 your copy.</p> <p>16 A Yes.</p> <p>17 Q Okay. And as I understand it, the copy</p> <p>18 that you brought with you here today that's now</p> <p>19 been marked as Exhibit 10 contains some</p> <p>20 corrections. Is that -- is that fair?</p> <p>21 A Yes.</p> <p>22 Q Could you please walk me through the</p> <p>23 corrections that you have made to your 2018 MDL</p> <p>24 report that has been marked as deposition</p> <p>25 Exhibit 10.</p>

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1 A Yes. So the first is on page 47. And  
2 in the first full paragraph that begins with  
3 "Table 9," on the fourth line --  
4 Q Let me pause you there for a moment,  
5 Dr. Siemiatycki. Are we both looking at page 47?  
6 A Now, I -- I'm not sure whether I printed  
7 this in a way that is not -- does not correspond  
8 to the version that you have. I'm sorry. I  
9 printed this just for my own use, so I didn't --  
10 Q No, looking at it, it looks similar.  
11 A Oh, okay.  
12 Q So why don't you direct me to the  
13 specific correction. I thought you were referring  
14 to the image of Table 9.  
15 MS. PARFITT: No, no. I think we're  
16 all on the same -- it's the same one you have --  
17 THE WITNESS: Okay.  
18 MS. PARFITT: -- on your thumb drives.  
19 THE WITNESS: Okay.  
20 BY MS. BRANSCOME:  
21 Q All right, we'll start again. So,  
22 Dr. Siemiatycki, if you could identify for me the  
23 corrections that you are making to your MDL report  
24 from November 2018.  
25 A Right. So on page 47, the first full

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1 paragraph, the fourth line, there are some  
2 numbers. It says "1.25," and then in parentheses,  
3 there is a 1.0 that was really a literal typo.  
4 Someone's -- my fingers were too heavy, and the  
5 one -- the first 1.0 should be dropped, and so the  
6 correct number is 1.15 to 1.36. Okay?  
7 The next one -- I'm sorry. Oh, the next  
8 one is on page 45, so a couple of pages earlier,  
9 in the second line -- are you with me? -- the  
10 sentence that begins "While the Terry 2013." It  
11 should be the Berge -- "While the Berge" -- the  
12 first Terry -- I'm just thinking out loud again.  
13 Whether in fact the Terry was the correct --  
14 anyway, yesterday when I was correcting this  
15 quickly, I thought that it -- that I had  
16 miswritten "Terry 2013" in that sentence and that  
17 it should have been Berge 2018.  
18 Do you mind if I look at this again at  
19 lunchtime and just verify which I was referring  
20 to? I'm now confusing myself about that.  
21 Q Not a problem. We can come back to that  
22 after -- either the next break or the lunch break.  
23 A And that -- those are the only  
24 corrections I picked up as I was going through it.  
25 Q I noticed as you were flipping through

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1 your copy of your report that there were other  
2 handwritten annotations.  
3 A Yeah.  
4 Q Can you please walk me through -- unless  
5 it's voluminous, in which case we can do it after  
6 a break -- any notations that you have made in  
7 your copy of your MDL report.  
8 A It's not voluminous. I didn't make  
9 many. One is on page 49. And in the middle of  
10 the page in italics, there is a misconception  
11 counting, et cetera, and just before that, I was  
12 talking about hospital-based studies and  
13 population-based studies. So the section that  
14 begins on page 48 is about hospital-based versus  
15 general population-based studies. And I made a  
16 note to myself after that -- at the end of that  
17 section, also --  
18 I mean, do you want me to quote what I  
19 wrote?  
20 Q Yes, please.  
21 A Sure. I said: "Also the basin for  
22 hospital controls may differ from the basin for  
23 cases."  
24 Q And what did you mean by that?  
25 A So, you're familiar with the idea, a

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1 hospital-based study? There are actually  
2 different types of hospital-based studies, which  
3 is something that has not come out in, really, in  
4 any of the discussion of this literature.  
5 But one of the problems with hospital-  
6 based studies is that when you choose a control  
7 group, let's say for a series of ovarian cancer  
8 cases from a given hospital, and you go to a  
9 different ward in that hospital to look for  
10 controls who are not -- don't have ovarian  
11 cancer -- the reasons for referral and the -- the  
12 pattern of patients coming to hospitals differs  
13 for different diseases. So serious -- it  
14 generally is the case that serious diseases in  
15 specialized hospitals tend to come from a wider  
16 geographic and social area than cases of traffic  
17 accident injuries or things that are treated in  
18 general hospitals more easily.  
19 And if you just take a series of cases  
20 of ovarian cancer and go to the emergency  
21 department to choose controls or you go to the GI  
22 surgery department where they do appendectomies  
23 routinely or something like that, you're picking  
24 up populations who are quite different.  
25 And this is one of the disadvantages of

<p style="text-align: right;">Page 66</p> <p>1 a hospital-based control strategy, and it's one of  2 the reasons why, in general, epidemiologists favor  3 population-based studies rather than hospital --  4 case control studies, population-based case  5 control studies, rather than hospital-based case  6 control studies, because the cases and the  7 controls -- one of the requisites in a case  8 control design is that the patients -- the cases  9 and the controls should represent the same study  10 base, the same basin of people who if they were  11 cases with the disease in question, ovarian  12 cancer, this is where they would end up, and all  13 of them would end up there.</p> <p>14 Q Are there any studies that were relevant  15 to your analysis for your MDL report that you  16 think this particular criticism that you have just  17 explained applies to?</p> <p>18 A I'm not sure. I didn't examine them  19 from that point of view.</p> <p>20 In this section of my report, it was  21 kind of a generic discussion of the issue of -- of  22 the merits of hospital-based versus population-  23 based studies.</p> <p>24 Q Okay. Do you have any other annotations  25 that you made in your copy of your MDL report?</p>	<p style="text-align: right;">Page 68</p> <p>1 THE VIDEOGRAPHER: We're going back on  2 the record at 11:41 a.m.</p> <p>3 BY MS. BRANSCOME:</p> <p>4 Q Do you have any other annotations there  5 with you on your copy of your report?</p> <p>6 A No. I have one other green sticky on  7 page 67, but there's nothing written on that page,  8 and I don't remember why I put that sticky there.</p> <p>9 Q Okay. The report that we just marked as  10 Exhibit 10, does that define the scope of your  11 opinions in the MDL?</p> <p>12 A The scope of my opinions. It defines my  13 opinions, yes.</p> <p>14 Q Does it contain all of the opinions that  15 you intend to offer at any trial or hearing in the  16 MDL?</p> <p>17 A I mean, I guess if I'm asked a question  18 that veers off from something I said in my report,  19 and I address the question, would that be  20 considered going off -- you know, offering an  21 opinion that is not in my report?</p> <p>22 It's just that -- I'm just not sure  23 about the technicality of your question. I mean,  24 I will offer -- I will answer questions even if  25 they lead off the content of my report.</p>
<p style="text-align: right;">Page 67</p> <p>1 A At the bottom of that same page, 49, I  2 wrote, quote, "Borenstein." And right now I'm --  3 oh, yes. So this misconception about counting the  4 number of statistically significant results as a  5 valid way of assessing consistency of results  6 among different studies is a basic flaw in the  7 conduct and interpretation of how to review a  8 series of studies.</p> <p>9 It's well known. I've known and I -- I  10 said it in my report that this is absolutely not  11 the way to synthesize evidence from multiple  12 studies, to count the number of significant ones.  13 And in addition to me saying it and many others, I  14 thought that I could -- if you asked me questions  15 about it or challenged my opinion on that score, I  16 could quote the textbook on meta-analysis, which  17 gives some good examples of why that's wrong.</p> <p>18 MS. PARFITT: Let's stop here for a  19 minute --</p> <p>20 MS. BRANSCOME: If we could go off the  21 record.</p> <p>22 MS. PARFITT: -- and go off the record.</p> <p>23 THE VIDEOGRAPHER: We're going off the  24 record at 11:39 a.m.</p> <p>25 (Pause.)</p>	<p style="text-align: right;">Page 69</p> <p>1 Q As you sit here today --</p> <p>2 A Yes.</p> <p>3 Q -- does the report that has been marked  4 as Exhibit 10 contain all of the opinions that you  5 have formed as of today about which you would  6 intend to testify at trial or a hearing on this  7 matter?</p> <p>8 A I -- I believe so.</p> <p>9 Q What was the question that you were  10 asked to answer in connection with the report you  11 generated in 2018?</p> <p>12 A I guess I -- I'll just refer back to  13 what it says in the report: "Can application of  14 talcum powder products in the perineal region  15 cause ovarian cancer?"</p> <p>16 Q Is that question different from the  17 question you were answering in your 2016 report?</p> <p>18 A I -- I don't see them as different.</p> <p>19 Q You would agree with me, though, that  20 there are differences between the report that you  21 produced in November 2018 and the report that you  22 produced in October 2016?</p> <p>23 MS. PARFITT: Objection. Form. Vague.</p> <p>24 THE WITNESS: Yes, there are some  25 differences.</p>

<p style="text-align: right;">Page 70</p> <p>1 BY MS. BRANSCOME: 2 Q When you began drafting the report 3 that's been marked there as Exhibit 10, your MDL 4 report, did you begin by using your 2016 report as 5 an initial draft? 6 A Yes. But I also had some ideas about 7 new things that I would want to do. Sort of 8 coming out of the Echeverria experience, I 9 realized that there were -- there were a couple of 10 errors in that -- my original report that I wanted 11 to correct. There were ways of doing the analyses 12 that, on reflection, I thought were not optimal 13 and that I could improve on, even if I anticipated 14 that the bottom line results would not change 15 much. But when I came to actually drafting the 16 text, I certainly used the previous report as a 17 primary source for revising -- for -- for drafting 18 the new one. 19 Q You mentioned that you wanted to make 20 some modifications because there were things in 21 the 2016 report that were either not optimal or 22 were errors. 23 Were any of the modifications that you 24 made done at the suggestion of plaintiffs' 25 counsel?</p>	<p style="text-align: right;">Page 72</p> <p>1 sequence, and I use both of them now but in 2 different places. 3 But -- so is your question, is it 4 exactly the same computer that all the files were 5 kept on or -- is that the sense of your question? 6 BY MS. BRANSCOME: 7 Q How about I ask it this way: Can you 8 describe for me the process by which you drafted 9 your 2018 report that's been marked as Exhibit 10? 10 A So I guess there were two parallel 11 things going on, or maybe more. One was to do 12 some reanalyses of the statistical meta-analysis. 13 And so that I initiated at a certain point 14 between -- probably in 2018. 15 At the same time, and I'm not sure if 16 this was after or before the statistical analyses 17 were started, I looked at the old draft. I 18 reviewed what was there, what I thought were 19 weaknesses in the way of expressing things or 20 things that could be brought to the report that 21 would enhance the clarity or the force of the -- 22 the exposition, and I started redrafting. So I'm 23 not sure if that answers your question. 24 Q Did you personally type the words that 25 are contained in Exhibit 10?</p>
<p style="text-align: right;">Page 71</p> <p>1 MS. PARFITT: Objection. 2 THE WITNESS: No. 3 BY MS. BRANSCOME: 4 Q So any of the changes that you made 5 between your 2016 report and the MDL report in 6 2018, were those all at your own prompting? 7 A Yes. 8 MS. PARFITT: Objection. Form. 9 THE WITNESS: Yes. 10 BY MS. BRANSCOME: 11 Q Did you work in the same computer file 12 to draft the 2018 report from start to finish? 13 MS. PARFITT: Objection. Form. 14 THE WITNESS: You're -- you're referring 15 to the text, not the statistical analyses, which 16 were done in a separate -- I mean, they -- they -- 17 the statistical analyses were based on the 18 addendum that I presented to you, and those are 19 kept on a FileMaker software, which is not on my 20 personal computer, but that my assistant has 21 access to. 22 But as far as the text is concerned -- 23 yeah, I think it was the same computer, but I've 24 changed computers since then, so I'm just 25 hesitating because I'm trying to think of the time</p>	<p style="text-align: right;">Page 73</p> <p>1 A All -- maybe all of them, and maybe 2 there were some paragraphs that I handwrote 3 because I was on a plane or a train, and when I 4 got back to the office, I asked someone to type up 5 that paragraph or two. But basically it was done 6 by me. 7 Q And did you save draft versions along 8 the way? 9 MS. PARFITT: Objection. Form. 10 THE WITNESS: Not really. Not -- 11 certainly not systematically. I didn't see any 12 reason to save discarded versions of things. 13 Yeah. 14 BY MS. BRANSCOME: 15 Q Did you conduct a new literature review 16 in connection with the 2018 report? 17 A I knew that I had all of the literature 18 that was pertinent and published as of 2016. 19 Updating what was available was partly done by 20 asking my research assistant to do a PubMed search 21 of anything new on the topic; asking the lawyers 22 if they had come across anything new in the past 23 year; my own antenna of knowing a lot of 24 epidemiologists and people who work in this area, 25 whether they are aware of anything. So sort of an</p>

<p style="text-align: right;">Page 74</p> <p>1 informal updating process from many branches.  2 Q Did plaintiffs' counsel provide you with  3 studies that had come out since you had generated  4 your 2016 report?  5 A I think they sort of pointed me to a  6 couple of things that I didn't have at the time.  7 I think one was the Penninkilampi review.  8 We're talking about the epidemiology  9 literature or everything? Because the  10 epidemiology literature I was pretty much in  11 control of through my networks and my people and  12 so on.  13 The stuff that I asked counsel to help  14 with was identifying literature in the areas of  15 toxicology, composition of talcum powder products,  16 mechanistic research that would bear on the issue.  17 So I asked them if they would provide me any new  18 data that they had available on those topics.  19 Q Do you consider yourself an expert in  20 toxicology?  21 A No. I'm sufficiently familiar to be  22 able to integrate the expertise of -- of real  23 experts.  24 Q Do you consider yourself an expert on  25 the composition of talc?</p>	<p style="text-align: right;">Page 76</p> <p>1 statistical analysis for your meta-analysis?  2 A It's -- I think it's called  3 Meta-Analysis, but -- it's called Comprehensive  4 Meta-Analysis, Version 3. It's listed in my  5 report on page 34.  6 Q And is that the only software that you  7 used to perform the statistical analyses in your  8 report?  9 A It's the only software that I used to  10 perform the meta-analyses. Are there any other --  11 I'm just trying to think if there are any other  12 analyses in the report besides meta-analyses or  13 statistical.  14 There were a couple of studies, and I --  15 I couldn't point them out just this minute, that  16 did not provide full information allowing -- that  17 didn't provide full information on odds ratios or  18 relative risks in a format that was useful for the  19 meta-analysis. And -- but they did provide the  20 numbers of cases and controls who were exposed and  21 unexposed. And that would typically -- I think in  22 at least one instance, maybe two, but at least one  23 instance, there was a situation where they  24 provided odds ratio estimates in different  25 categories of usage of talc or either different</p>
<p style="text-align: right;">Page 75</p> <p>1 A No.  2 Q And do you consider yourself an expert  3 on potential biological mechanisms of the  4 development of ovarian cancer?  5 A No.  6 Q Other than being aware of the opinions  7 of others in those particular fields, are you  8 offering any expert opinions in toxicology, the  9 composition of talc, or the biological mechanism  10 by which ovarian cancer may develop?  11 A I'm --  12 MS. PARFITT: Objection. Form.  13 Go ahead.  14 THE WITNESS: I'm -- I reviewed the  15 information that I was provided, and I took note  16 of the types of evidence that are available in  17 those domains, and I used it mainly in thinking  18 about biological plausibility of the association.  19 It -- those areas of evidence did not in any way  20 influence my opinions about the strength and  21 consistency and so on of the epidemiological  22 evidence.  23 BY MS. BRANSCOME:  24 Q Did you -- oh, before I forget, what is  25 the name of the software that you used to do the</p>	<p style="text-align: right;">Page 77</p> <p>1 durations or different amounts used per day or  2 something like that, but didn't summarize that in  3 an overall ever-used-it-at-all versus  4 never-used-it, which was what I was looking to use  5 in the meta-analysis.  6 And I think in those -- in that  7 instance, I did almost a hand calculation.  8 Because it's pretty straightforward how you do  9 this, just re- -- picking the numbers in their  10 tables and recalculating the overall odds ratio.  11 But this is a few years ago, and I --  12 I -- I would have to go back and review that, but  13 it was -- I think in the other meta-analyses,  14 Berge and Penninkilampi, which were carried out  15 completely independently of mine, and I didn't  16 know about theirs, I think they had to do  17 something similar and arrived at the same answers.  18 So -- but, no, I mean there was no -- no  19 other statistical package used. That kind of  20 calculation can be done by hand.  21 Q How would -- how would I, if I'm looking  22 at your report, identify which studies you  23 actually calculated the odds ratio or relative  24 risk that you input into your meta-analyses?  25 A I -- I -- I'd have to look at it at</p>

<p style="text-align: right;">Page 78</p> <p>1 lunchtime, if you don't mind, and see if there was 2 one.</p> <p>3       There was one. I don't know if that was 4 retained in the end or if -- I'm sorry. It's --</p> <p>5       Q   When you say you don't know if a study 6 was retained in the end, are there studies that 7 you considered including in your meta-analysis and 8 ultimately did not?</p> <p>9       A   Only if they didn't provide evidence on 10 the relationship between talcum powder used in the 11 perineal area and ovarian cancer.</p> <p>12       Q   All right. If you wouldn't mind looking 13 at that at lunch, we will come back --</p> <p>14       A   Yes. Thank you.</p> <p>15       Q   -- to that after the lunch break.</p> <p>16       THE WITNESS: Someone make a note for 17 me.</p> <p>18 BY MS. BRANSCOME:</p> <p>19       Q   Did you --</p> <p>20       MS. PARFITT: Yes, a note.</p> <p>21 BY MS. BRANSCOME:</p> <p>22       Q   Did you personally conduct the 23 meta-analysis that was performed as part of your 24 2018 report?</p> <p>25       A   No, I did not do the --</p>	<p style="text-align: right;">Page 80</p> <p>1 from one to another was perfectly in line with 2 what I would expect.</p> <p>3       Furthermore, the results that we 4 obtained are almost identical to the results that 5 others have independently obtained doing 6 meta-analyses on these topics using basically the 7 same studies. Sometimes the difference of -- 8 minor differences of which result from each study 9 they selected, but basically the results are so 10 similar that I'm confident that there was no 11 glitch.</p> <p>12       Q   Did you save the results of these 13 sensitivity analyses?</p> <p>14       A   Do you mean the output from the computer 15 software for each one? Is that what you're --</p> <p>16       Q   Is there any way from the materials that 17 you have produced in connection with your report 18 for someone to replicate the sensitivity analyses 19 that you performed?</p> <p>20       MS. PARFITT: Objection. Form.</p> <p>21       THE WITNESS: Well -- I reproduced in 22 the report a few plots of -- that come straight 23 out of the program. So for those, it's absolutely 24 replicatable. Anybody can then go to the package 25 and put -- punch in the same input, and they'll --</p>
<p style="text-align: right;">Page 79</p> <p>1       Q   Who did that?</p> <p>2       A   My student.</p> <p>3       Q   And what is your student's name?</p> <p>4       A   Mengting, M-E-N-G-T-I-N-G, Xu, X-U.</p> <p>5       Q   And -- and what are -- is it Mr. or 6 Dr. Xu?</p> <p>7       A   It's -- she's a Ph.D. student at the 8 moment. She will be a doctor.</p> <p>9       Q   What are her qualifications for 10 conducting a meta-analysis?</p> <p>11       A   She is very skilled at statistical 12 analyses and at -- at computer packages. I'm not 13 sure if she's taken a course in meta-analysis 14 specifically, but it's not rocket science to do 15 that with a package like the one we have.</p> <p>16       Q   Did you verify that the meta-analysis 17 was performed correctly using the software?</p> <p>18       A   I looked at the results in various ways 19 to assure myself that everything looked good. By 20 looking good, I mean that there was internal 21 coherence, like she carried out many different 22 meta-analyses under different conditions and -- 23 not different conditions, but including some 24 studies and excluding studies -- these are called 25 sensitivity analyses -- and the pattern of results</p>	<p style="text-align: right;">Page 81</p> <p>1 they'll get the same output. For the -- I didn't 2 do that for every single sensitivity analysis, 3 just for economy -- to save the reader the burden 4 of that. But I'm pretty sure -- I'm pretty sure 5 that Mengting kept files of each of those 6 analyses.</p> <p>7 BY MS. BRANSCOME:</p> <p>8       Q   Did anyone else -- you mentioned a 9 research assistant helped you with PubMed 10 searches. Who was the research assistant?</p> <p>11       A   She's a woman, who was with me for 30 12 years or so, who was basically the bibliographic 13 expert in our team and helped people find articles 14 and do things necessary, like PubMed searches and 15 so on. So she -- while she was here -- she 16 retired a year or so ago. While she was here, I 17 asked her to look at the ovarian cancer/talc 18 thing, and she dug out some -- she found some 19 articles for me.</p> <p>20       Q   Is that Sally Campbell?</p> <p>21       A   Yes, it is.</p> <p>22       Q   Okay. After Ms. Campbell retired, did 23 anyone else help you perform literature searches?</p> <p>24       A   Not in a routine way for sure. If I 25 wanted to find a specific article that I knew</p>

<p style="text-align: right;">Page 82</p> <p>1 about, I would typically ask my student Mengting 2 to dig it out and print it for me. 3 Q So in addition to Ms. Campbell and 4 Ms. Xu -- 5 A Xu, yes. 6 Q -- did anyone else help prepare the 7 materials that are in your 2018 report? 8 A Yes. So I have another research 9 assistant who's been with me even longer than 10 Sally Campbell, who retired a month ago, and her 11 name is Lesley Richardson. And she set up and 12 maintained the database system in which we 13 integrated all of the results that are in that 14 addendum that I provided you, and that involved 15 reviewing each article and taking every single 16 result and plugging it into this software. 17 Q Did Ms. Richardson exercise any of her 18 own judgment in selecting which data to include in 19 the meta-analyses? 20 A The instruction was to extract 21 everything. Simple instructions can become 22 difficult in operation. And some of the 23 frustration in this area and some of the reason 24 why there is some variability in which studies and 25 which results are included in different</p>	<p style="text-align: right;">Page 84</p> <p>1 Q Okay. And you mentioned reviewing the 2 materials that came out in connection with Health 3 Canada and the Taher manuscript, and we'll talk 4 about that in more detail, but did anything you 5 reviewed since the production of your 2018 report, 6 has any of that changed your opinions or any of 7 the information that is contained in your MDL 8 report? 9 A It doesn't really change anything. I 10 would say that the Health Canada report reinforces 11 the notion that this issue is becoming a front 12 burner issue for public health agencies. But 13 it -- since I didn't explicitly address that 14 question in my report, I would say it doesn't 15 change anything that's in my report. 16 Q Do you intend to offer expert opinions 17 about the different positions of the different 18 public agencies and the relative importance of a 19 potential connection between talc and ovarian 20 cancer? 21 MS. PARFITT: Objection. Form. 22 THE WITNESS: Did I intend -- while 23 writing my report, do you mean, to make -- no. I 24 don't think that those agencies and those 25 positions necessarily reflect the most up-to-date</p>
<p style="text-align: right;">Page 83</p> <p>1 meta-analyses occur because authors are sometimes 2 cryptic about what they say about their data and 3 their results. And specifically things like what 4 kind of talc use a certain table describes is not 5 always perfectly clear. 6 And so she would need to make a judgment 7 sometimes as to whether this result pertained to 8 all use of talc in the perineal area or only 9 powdering, excluding sanitary napkins or other -- 10 sometimes it -- there's ambiguity in the write-up 11 of these things that therefore requires -- 12 required some judgment on her part. And several 13 of these things she would ask my opinion about, 14 and we would discuss it and say, Well, it looks 15 like this or it looks like that, and let's go with 16 this interpretation. 17 Q Okay. And at the end of the day, 18 despite receiving help from others in developing 19 your 2018 report, do you personally stand behind 20 everything that is in the report? 21 A Yes. Barring more typos. I know that 22 every time I look at anything I've ever written 23 or, you know, things that are expressed not in the 24 most clear way. But, yes, I stand behind 25 everything.</p>	<p style="text-align: right;">Page 85</p> <p>1 science, and I think the most up-to-date science 2 is in the science community through publications 3 and so on, and public health policies tend to lag 4 behind scientific knowledge. 5 BY MS. BRANSCOME: 6 Q Are there instances where public health 7 policies are more conservative than the scientific 8 literature out of sort of a principle of 9 precaution? 10 MS. PARFITT: Objection. Form. 11 THE WITNESS: Sorry, I'm not sure I 12 understand the question. 13 BY MS. BRANSCOME: 14 Q Sure. 15 Are there examples where the public 16 health policy is actually, for instance, more 17 protective than the science might support because 18 the public health agency is exercising an 19 abundance of caution? 20 MS. PARFITT: Objection. Form. 21 THE WITNESS: I -- I believe so. I 22 mean, I've not done any kind of survey of how 23 public health policy in, you know, Sweden over 24 Argentina or everywhere -- you're talking about 25 generally in the world public health or are you</p>

<p style="text-align: right;">Page 86</p> <p>1 talking about United States or -- but I -- I  2 imagine there are instances like that, and I think  3 there is a strand in public health to be  4 precautionary in developing policies. But I'm not  5 sure it's universal. I just don't know.  6 BY MS. BRANSCOME:  7 Q You have a References section in your  8 report. It begins at page 109, if you need to  9 refer to it.  10 How did you maintain all of the  11 documents that are identified under that list?  12 It's quite voluminous.  13 A So let me --  14 Q And by that, I mean did you keep hard  15 copies? Do you keep electronic copies?  16 A Okay. So the first thing I'll point out  17 is that I deliberately didn't call it a reference  18 section. You'll see that it's called a  19 Bibliography.  20 Q Could you turn to page 109 in your  21 report.  22 A That -- that's where I am.  23 Q Could you turn to the page right before  24 that.  25 A Oh. Ah, yes, I see that.</p>	<p style="text-align: right;">Page 88</p> <p>1 A So, yeah, yeah.  2 Q -- Dr. Siemiatycki, is how -- how do you  3 maintain all of the documents that are listed in  4 your reference section? Do you main hard copies?  5 Do you keep electronic copies?  6 A It's a bit of a mix and match of  7 electronic and hard copies. And these are all the  8 materials that were collected over the years, you  9 know, I would say from the beginning of my  10 involvement in the previous trial and so on, that  11 concern talc and ovarian cancer, including  12 materials that were provided by the lawyers and  13 materials that we found.  14 I prefer to work with paper -- I prefer  15 to read paper, but at a certain point, that gets  16 overwhelming, and the material -- I can't tell you  17 right now for sure that everything here is -- that  18 I have it electronically in a file or that I have  19 it in paper.  20 Q There are different sections of your  21 References section. You have Bibliography Part A,  22 B, so on and so forth. Who made the decision of  23 which articles or documents fell into which of  24 the -- of each category?  25 A I -- I guess I made it, but it was</p>
<p style="text-align: right;">Page 87</p> <p>1 Q What is the page -- you have that as  2 page 108?  3 A Yes, I have that page with the word  4 "References" on page 108. Section 16.  5 Q Perhaps we could check at the break. My  6 page numbering got off of yours at some point.  7 A Okay.  8 Q But in any event, you do have a  9 Section 16 that's titled "References," correct?  10 A Yes. Yes, I do. I do.  11 Okay. My -- my conscious volition was  12 to call this a bibliography, and the word  13 "references" got in -- into the heading of this  14 section.  15 And the reason for that distinction is  16 that I have not -- not everything that is listed  17 is referred to in the text of my report. So  18 technically speaking, a reference section should  19 be those materials that you refer to in your  20 report. And this is not what I have here. And  21 that's why I -- consciously I wanted to call this  22 a bibliography, and somehow the word "references"  23 got -- when they -- when we were compiling it --  24 anyways.  25 Q Okay. So my question again --</p>	<p style="text-align: right;">Page 89</p> <p>1 pretty self-evident. The material in Part A is  2 material that is generally publicly available.  3 It's easy to identify that. And the materials in  4 Part B is material that is not publicly available.  5 And all of that came from the lawyers, I think.  6 Q So that was going to be one of my  7 questions. Did all of the materials identified in  8 Bibliography Part B come to you from plaintiffs'  9 counsel?  10 A Okay. So let me look through this  11 quickly.  12 MS. PARFITT: Mm-hmm. Go ahead.  13 THE WITNESS: (Peruses document.)  14 I think so. I -- I think all of it came  15 from plaintiffs' counsel.  16 BY MS. BRANSCOME:  17 Q I'm not going to ask you about all of  18 these, but I noticed on page, at least in my copy,  19 135, maybe 134 on yours, there's reference to the  20 Berg v. Johnson &amp; Johnson case.  21 Do you see that?  22 A Yes, I see that.  23 Q What relevance is it to you as an  24 epidemiologist evaluating the potential risk of  25 ovarian cancer from perineal use of talc to look</p>

<p style="text-align: right;">Page 90</p> <p>1 at the final jury instructions, judgment, and 2 verdict form from the Berg case? 3 A I'm not sure. I relied on plaintiffs' 4 counsel to decide what they thought it would be 5 pertinent for me to be aware of. So these were 6 documents that they thought would be pertinent for 7 me to -- to be aware of, and I can't say why, and 8 I don't remember -- frankly, I don't remember 9 these documents. 10 Q As a scientist, do you typically 11 consider jury instructions in forming an opinion 12 with respect to risk of the use of a product in 13 epidemiology? 14 MS. PARFITT: Objection. 15 THE WITNESS: Outside of a legal -- no, 16 we wouldn't have access to it or -- no, it never 17 comes up. 18 BY MS. BRANSCOME: 19 Q As you sit here today, can you come up 20 with any reason why the jury instructions in a 21 case would be relevant to you in evaluating the 22 question you were asked to answer, which is 23 whether or not there is a risk of ovarian cancer 24 from the perineal use of talc? 25 MS. PARFITT: Objection. Form.</p>	<p style="text-align: right;">Page 92</p> <p>1 informative of your opinions? 2 A No. There's no way for anyone else to 3 know that. 4 Q Okay. Did you ask plaintiffs' counsel 5 for specific company documents, using that term 6 loosely, to refer to documents that are kept 7 internally within the various companies at issue 8 in this litigation? 9 A I asked to be sent any information they 10 had about the composition of talcum powder 11 products, historically as well as currently, but 12 actually mainly historic -- I was mainly 13 interested to know what was the history of the 14 composition of talcum powder products. 15 And so many of these materials that they 16 sent me -- and I can't tell you which ones because 17 I don't identify them with these obscure numbers, 18 they don't mean anything to me -- but some of them 19 dealt with internal company documents or internal 20 reports that discussed different types of talc -- 21 of powdering products, whether talc products or 22 cornstarch products in different eras, when they 23 started and when, what the market share was in 24 different eras. So I was interested in that to 25 get a sense of what were the women exposed to who</p>
<p style="text-align: right;">Page 91</p> <p>1 THE WITNESS: You're asking me to 2 speculate as to why plaintiffs' counsel would have 3 sent this to me? 4 BY MS. BRANSCOME: 5 Q I'm asking -- 6 A Is that what you're asking? 7 Q I'm asking if you, as the scientist 8 whose name is on this expert report, can you think 9 of any reason why that would be informative to you 10 as a scientist? 11 A If I had it in front of me, I might 12 recognize something in there that would make it 13 relevant. But I -- I don't know what is typically 14 in such jury instructions. I don't know how -- 15 what the sweep is of those things. I'm just not 16 sure. So I -- I can't answer the question. 17 Q As you sit here today, do you recall 18 reading the final jury instructions from Berg -- 19 A I don't -- 20 Q -- v. Johnson &amp; Johnson? 21 A I don't actually recall reading it. 22 Q Okay. So is there any way for someone 23 reviewing your report to identify within the 24 reference section, Part B, which of these 25 documents you, Dr. Siemiatycki, found relevant and</p>	<p style="text-align: right;">Page 93</p> <p>1 were part of these epidemiologic studies. 2 Q Do you rely on any of the information 3 that you obtained from documents in Part B of your 4 reference list as a basis for forming your expert 5 opinion in the MDL? 6 A No. No. 7 Q Have you viewed any of the deposition 8 transcripts of the depositions that have been 9 taken in the MDL? 10 A I have looked at a few of them. 11 Q And which deposition transcripts have 12 you reviewed? 13 A Plunkett, McTiernan, is it? And Singh. 14 Not fully -- not the entire transcripts, but 15 portions thereof. Blount. I've seen excerpts 16 from, is it, Hopkins? And a table from Pier, but 17 not the full text. I didn't review the full text 18 -- transcript. There may be one or two more, and 19 I can't recall right now. 20 Q Okay. Focussing specifically on the 21 expert deposition transcripts from the MDL, did 22 you ask specifically for Drs. Plunkett, McTiernan 23 and Singh's deposition transcripts? 24 A I didn't know who the other experts 25 were, so I didn't ask for them by name. And I</p>

<p style="text-align: right;">Page 94</p> <p>1 think that I asked if they could share with me 2 transcripts of depositions and reports. So I also 3 had some of the reports from those experts. I'm 4 not sure I had all of them but at least some of 5 them. 6 Q Well, what materials had you reviewed 7 with respect to other experts in the MDL before 8 you completed your report that we've marked as 9 Exhibit 10? 10 A None. All of what I've just described 11 was after I completed my report. 12 Q Did you rely on the work or opinions of 13 any other expert witnesses in forming your own 14 opinions in the MDL? 15 A No, I don't think I did. 16 Q So understanding that more depositions 17 have been taken than just Drs. Plunkett, McTiernan 18 and Singh, what specifically was your request to 19 plaintiffs' counsel for which deposition 20 transcripts you would like to see? 21 MS. PARFITT: Objection. Asked and 22 answered, form. 23 THE WITNESS: I'm not sure if my request 24 was to see the ones that they thought were most 25 relevant to -- to me or whether I specifically</p>	<p style="text-align: right;">Page 96</p> <p>1 I specifically asked at some point to be provided 2 with information that would inform on the presence 3 of asbestos fibers in talcum powder products. 4 BY MS. BRANSCOME: 5 Q Did you review that material before 6 completing your MDL report? 7 MS. PARFITT: Do you understand the 8 question? 9 THE WITNESS: Yeah. 10 Yes, I think I did look at that before 11 completing my report. 12 BY MS. BRANSCOME: 13 Q When you say the asbestos is an issue 14 that has come up in the last few months, what do 15 you mean by that? 16 A Well, my understanding back in 2016, 17 '17, was that while asbestos had been detected in 18 talcum powder products as far back as the '70s -- 19 1970s, there was an industry directive or promise 20 or instruction that they would somehow get rid of 21 the problem of asbestos contamination. 22 Q And what was your basis for that 23 understanding? 24 A I guess things I've read, and possibly 25 in some of the company documents, possibly in</p>
<p style="text-align: right;">Page 95</p> <p>1 said the epidemiology ones, but I think probably 2 the former, because they sent me, for example, 3 Dr. Plunkett, who is not an epidemiologist. Yeah. 4 BY MS. BRANSCOME: 5 Q Which expert reports have you reviewed 6 that are from the MDL? 7 A I looked at the Plunkett report. I 8 think I looked at the Singh and the McTiernan 9 report. But just dipping into it, not -- not 10 reading it fully. Yeah. 11 Q Any other reports? 12 A Not that I recall offhand. 13 Q Okay. The Blount transcript, the 14 Hopkins transcript, and the table from Julie 15 Pier's deposition, were those items that were 16 provided to you by plaintiffs' counsel? 17 A Yes. 18 Q Did you request them specifically or 19 were they simply given to you? 20 MS. PARFITT: Objection. Form. 21 THE WITNESS: I requested them to 22 provide me with information that would help me to 23 understand the issue. And one of the issues that 24 has come up in the past few months was the issue 25 of asbestos in talcum powder products, and I think</p>	<p style="text-align: right;">Page 97</p> <p>1 publications. I think there have been various 2 publications that have said so that have -- and I 3 can't right now point to those, but that for the 4 last 10 or 20 years have said that asbestos 5 contamination may have been a problem up to the 6 1970s, but that the industry has basically managed 7 to eliminate that contamination. So I've read 8 that, and it seemed to be repeated often enough 9 that I came to take it as a fact. 10 And then I received some -- I guess I 11 received some reports from plaintiffs' counsel of 12 some new studies carried out more recently in 13 the -- by Longo and his team, and some others, put 14 in question whether asbestos fibers were present 15 in talcum powder products. And so this caused me 16 to revisit that whole thing. 17 My opinions offered in 2016, '17, about 18 talc and ovarian cancer were premised on the 19 assumption that whereas there may have been some 20 contamination up to the 1970s, it was basically a 21 nonissue after the 1970s. So the opinions I 22 expressed in -- in 2016, '17, were independent of 23 any hypotheses about asbestos in talc. 24 When I saw the reports from Longo and 25 maybe others in the fall -- I think it was in the</p>

<p style="text-align: right;">Page 98</p> <p>1 fall of 2018, I specifically asked counsel to 2 provide me with other information that they had, 3 and I made a point of saying, you know, Are there 4 studies that contradict these -- is there evidence 5 that contradicts these evidence -- these claims of 6 asbestos contamination? And they sent me some 7 material at that point. 8 Q Okay. The work that Dr. Longo had 9 conducted with respect to analyzing talcum powder 10 products, to your knowledge, has that ever been 11 published? 12 A I'm not sure. I -- to my knowledge, no, 13 but maybe it has been. I don't know. 14 Q Okay. What were you -- when you 15 referred to the study that Dr. Longo conducted, 16 what -- are you referring to the work that he has 17 done in connection with litigation on behalf of 18 plaintiffs' counsel? 19 A I'm referring to a few reports that I 20 think are dated or -- not -- 2017, 2018. I guess 21 they're connected to litigation, but I'm -- I'm 22 not absolutely certain of that. But those are -- 23 that's what I'm referring to. 24 Q Separate and apart from your role as an 25 expert witness, when you're evaluating a</p>	<p style="text-align: right;">Page 100</p> <p>1 of the investigators. I know many of the people 2 in the area that I work in, and I can -- often 3 have a gut feeling about the quality of their 4 work. 5 Q Do you know anything about Dr. Longo's 6 qualifications such that you could render an 7 opinion about the quality of his work? 8 A It's in a different area than mine, so 9 the answer is I -- I couldn't render an opinion 10 about it. 11 Q When you asked for evidence that might 12 contradict the work that Dr. Longo had done in 13 connection with litigation, what specifically were 14 you provided by plaintiffs' counsel? 15 A I'm sorry, without digging around and 16 looking at e-mail exchanges, offhand I can't tell 17 you. I was provided with a batch of -- of 18 documents. I can't remember how many were on one 19 side or the other side. I remember there -- well, 20 in my report I refer to a few pieces of evidence 21 that -- yes. So -- can I -- well, on page 30 in 22 my copy -- 23 Q Okay. 24 MS. PARFITT: Why don't you give the 25 category, the title.</p>
<p style="text-align: right;">Page 99</p> <p>1 scientific question, do you typically consult 2 expert reports that are generated for purposes of 3 litigation? 4 MS. PARFITT: Objection. Form. 5 THE WITNESS: I would -- if I had 6 access -- I mean, usually we don't know about such 7 reports if we're not in the litigation process. 8 So it's a hypothetical question, I guess. It -- 9 it just doesn't come up in reality that I would be 10 looking at carcinogenicity of diesel engine 11 emissions, and I would have access to reports 12 produced in litigation that are not published. 13 I -- I don't know that I -- I wouldn't have access 14 to such information unless I was part of the 15 litigation. But... 16 BY MS. BRANSCOME: 17 Q Okay. When you're evaluating scientific 18 literature, do you place a different amount of 19 weight on a study that has been peer reviewed as 20 compared to one that has not? 21 A Yes, it's one of the considerations. 22 Q Okay. And -- 23 A There -- there are many considerations 24 that I weigh, including my knowledge of and 25 evaluation of the skill and reputation and quality</p>	<p style="text-align: right;">Page 101</p> <p>1 THE WITNESS: Oh, the -- so it's in 2 Section 5.3.2, "What were women exposed to in body 3 powders?" 4 BY MS. BRANSCOME: 5 Q Were you provided, for example, with the 6 expert reports generated by the expert retained by 7 Johnson &amp; Johnson and Imerys to rebut Dr. Longo's 8 report? 9 A Can you give me the author's name or -- 10 Q Sure. Were you provided any reports by 11 Dr. Matthew Sanchez? 12 A I don't recall. I don't recall that. 13 Q Are you offering an expert opinion about 14 the contents of any of the talcum powder products 15 sold or manufactured by Johnson &amp; Johnson? 16 A I only take note of what has been 17 provided in the various documents I have access 18 to. 19 Q What does that mean? 20 A It means -- can I read the sentence? 21 Basically, I think it summarizes what I mean. And 22 I'll start -- so I'll start on the sentence that 23 on my copy is on the bottom of page 29, still in 24 that Section 5.3.2. 25 "So representatives of the industry have</p>

<p style="text-align: right;">Page 102</p> <p>1 claimed that talcum powders were free of asbestos  2 fibers since the 1980s" -- and there are a couple  3 of references there --  4 MS. PARFITT: Read them.  5 THE WITNESS: "Hopkins 2018, Pier 2018.  6 -- "but this assertion has increasingly  7 come under doubt as a number of labs have reported  8 finding asbestos fibers in talcum powder  9 products." And it references Blount, '91;  10 Paoletti, '84; Gordon, 2014; Longo, et al., 2017  11 and 2018; Blount deposition, 2018; Pier  12 deposition, 2018.  13 "These various studies that have  14 reported finding asbestos in historic talcum  15 powder samples have been challenged by other  16 reports that failed to find meaningful amounts of  17 asbestos in historic talcum powder samples." And  18 the two citations are CIR 2013 and Anderson 2017.  19 BY MS. BRANSCOME:  20 Q So what I'm trying to understand,  21 Dr. Siemiatycki, is what role this information  22 plays in your opinions, if any.  23 A Not much. You know, I would say that  24 the -- my opinions about the association are  25 driven by the strength and consistency of the</p>	<p style="text-align: right;">Page 104</p> <p>1 and answered.  2 THE WITNESS: You know, I would say the  3 sentences that I read summarize my opinion on that  4 question.  5 BY MS. BRANSCOME:  6 Q So in your opinion, is it -- is it a  7 question for debate in the scientific community at  8 the moment?  9 MS. PARFITT: Objection. Form.  10 Misstates his testimony.  11 THE WITNESS: It's not an area in which  12 I feel confident to pronounce that the issue has  13 been resolved or not.  14 MS. BRANSCOME: Is now a good time for a  15 break? I don't now how long --  16 MR. TISI: We've been going about an  17 hour and 25 minutes.  18 MS. PARFITT: We have lunch at 1:00, and  19 I don't think it's here.  20 (A discussion was held off the record.)  21 MS. BRANSCOME: We can go off the  22 record.  23 THE VIDEOGRAPHER: This ends disc number  24 in the deposition of Jack Siemiatycki. We're  25 going off the record at 12:42 p.m.</p>
<p style="text-align: right;">Page 103</p> <p>1 epidemiologic evidence. And this information  2 about asbestos contamination of talcum powder  3 products would be capable of moving the dial in  4 the direction of increasing my belief that there  5 is a causal assoc- -- a causal relationship, if it  6 is demonstrated that there were in fact asbestos  7 fibers contaminating.  8 So if it is shown that they are present,  9 that would increase my level of belief. If it is  10 not shown, if it is not demonstrated, it would not  11 detract from my finding based on the epidemiologic  12 evidence. It could move the dial in one  13 direction. It wouldn't move the dial in another,  14 because there -- there are different conceivable  15 ways that talcum powder products could increase  16 the risk of ovarian cancer. This is one. I'm not  17 capable of adjudicating whether this one is  18 correct or not.  19 Q So as you sit here today,  20 Dr. Siemiatycki, do you have an opinion to a  21 reasonable degree of scientific certainty that  22 there are in fact contaminants like asbestos or  23 heavy metals in Johnson &amp; Johnson's talcum powder  24 products?  25 MS. PARFITT: Objection. Form. Asked</p>	<p style="text-align: right;">Page 105</p> <p>1 (Lunch recess.)  2 THE VIDEOGRAPHER: This begins disc  3 number 3 in the deposition of Jack Siemiatycki.  4 We're going back on the record at 1:46 p.m.  5 BY MS. BRANSCOME:  6 Q Good afternoon, Dr. Siemiatycki.  7 Did you have a chance to look at the  8 various subjects we were going to return to after  9 the lunch break?  10 A I did.  11 Q Okay. So we'll take them one at a time.  12 A Yes, please.  13 Q Let's start first with, did you identify  14 the document that you had been provided by  15 plaintiffs' counsel that you said you took out all  16 but about 20 pages that you found relevant?  17 A Right. So I -- I think I mentioned the  18 IARC monographs as being two of them, and I think  19 the third one was the Reference Manual on  20 Scientific Evidence. There was a huge pack of  21 pages that were sent to me, and I took out most of  22 them, but I retained some that I thought were  23 relevant.  24 Q What portions of the Reference Manual on  25 Scientific Evidence did you retain?</p>

<p style="text-align: right;">Page 106</p> <p>1 A I think it was the Epidemiology section 2 and maybe the Statistics section. 3 Q All right. During the break, you were 4 also going to check which of the epidemiological 5 studies that you included in your meta-analysis. 6 Did you or someone at your direction 7 independently calculate an odds ratio or relative 8 risk figure that was not published in the report 9 itself? 10 A Sorry, what? That was not published in 11 the original report. So I'm not sure. The answer 12 is in the time I had available, I couldn't really 13 identify anything like that, and I'm not sure if 14 that occurred at all, and it -- the impact of 15 that, if -- if it had occurred, would have been 16 negligible. 17 Q If -- 18 A It would have meant -- I'm sorry. It 19 would have meant that most likely I added -- I put 20 together a two-by-two table by aggregating across 21 two or three or four levels of exposure. If -- if 22 it had happened, I think that's what would have 23 happened. And the impact of that would be to 24 produce an odds ratio estimate that is not 25 adjusted for the covariates that they adjusted for</p>	<p style="text-align: right;">Page 108</p> <p>1 think what it is, we've got the signature page on 2 the one report, and then the one he has in his 3 binder appears to not have a signature page on it, 4 and the font seems to be -- when the signature 5 page was put in, the font was slightly larger, 6 which sort of throws off the page numbers. Same 7 report. 8 MS. BRANSCOME: So what I would -- 9 MS. PARFITT: Single -- 10 MS. BRANSCOME: -- request so that we 11 keep the record clean going forward and not every 12 question has to say page 108 in mine and page 107 13 in your copy is that we actually mark the version 14 of the report that has been produced to us as 15 Exhibit 11 -- well, let me just, Ms. Parfitt, 16 would you be comfortable marking his copy as 17 Exhibit 11 and switching them and putting the new 18 clean copy as Exhibit 10? I'm only thinking that 19 there are many prior questions -- 20 MS. PARFITT: Sure, I'm fine with that. 21 MS. BRANSCOME: -- that refer to his 22 report -- 23 MS. PARFITT: As long as his -- 24 MS. BRANSCOME: -- as Exhibit 10. 25 MS. PARFITT: Yeah, and just so the</p>
<p style="text-align: right;">Page 107</p> <p>1 in their analysis by the categories of dose or 2 whatever they adjusted for. 3 Q Is there any way by examining your 2018 4 report and the addendum that an outside reader 5 could determine which studies, if any, were 6 subject to this independent calculation? 7 A So the one thing I didn't check during 8 the break was whether there's a note in the 9 addendum, and it would take me a while, I'd have 10 to go through each study and see if there's any 11 notation in the margin that would indicate that 12 this was done. So I -- I -- I'm not sure of the 13 answer to your question. 14 Q If an adjustment like that or an 15 independent calculation had been done, would it be 16 your expectation that a notation would have been 17 made in the addendum? 18 A Yes. Yes. 19 Q All right. Did you look at anything 20 else over the lunch break? 21 A Well, we looked to see -- the page -- 22 pagination discrepancy between the different 23 versions, and I think Ms. Parfitt could fill you 24 in on -- or maybe she has. I don't know. 25 MS. PARFITT: No. No, I haven't. I</p>	<p style="text-align: right;">Page 109</p> <p>1 record is clear, and what appears to have happened 2 is there was a signature page that was put on the 3 report to represent the matter was filed in the 4 United States District Court, the District of New 5 Jersey, in light of the prior report that was in a 6 state court, and that has thrown off not only the 7 page numbers but I think even it might have been a 8 different font. 9 Sure, so we will put on -- 10 THE WITNESS: So do you want to modify 11 the -- this? 12 MS. PARFITT: Sure. I think what we're 13 going to do is the one that Dr. Siemiatycki has 14 brought will be now Exhibit 11, and the one that's 15 in -- on the thumb drive and -- 16 MS. BRANSCOME: It is tab 3 in the 17 binder in front of you will be the correct 18 Exhibit 10. 19 MS. PARFITT: And this will be 20 Exhibit 11. 21 MR. TISI: And Exhibit 11 will be his 22 copy, the one that he brought. 23 MS. PARFITT: And this will be 3 -- 3, 24 correct? 25 MS. BRANSCOME: 11 -- I mean 10. It's</p>

<p style="text-align: right;">Page 110</p> <p>1 tab 3.</p> <p>2 MS. PARFITT: 11 -- 10. Tab 3, correct.</p> <p>3 (Exhibit No. 11 was marked for</p> <p>4 identification.)</p> <p>5 BY MS. BRANSCOME:</p> <p>6 Q So, Dr. Siemiatycki, can you confirm</p> <p>7 that Exhibit 10 is a complete copy of your report</p> <p>8 that was submitted in the MDL? It is a clean copy</p> <p>9 and does not contain any annotations.</p> <p>10 A Yes.</p> <p>11 Q Can you also confirm that what we have</p> <p>12 now marked as Exhibit 11 is the copy of your MDL</p> <p>13 report that you brought with you here today? It</p> <p>14 does contain handwritten annotations and the page</p> <p>15 numbers are just slightly misaligned.</p> <p>16 A Yes.</p> <p>17 Q Okay. So if you could, in Exhibit --</p> <p>18 oh, there was one other --</p> <p>19 A There was one other, and -- and there's</p> <p>20 another -- yet another one that I -- a correction</p> <p>21 to be made, a small one.</p> <p>22 So do you want to point out what that --</p> <p>23 Q Yes. So, Dr. Siemiatycki, do you have</p> <p>24 any corrections that you would like to make to</p> <p>25 your report at this time?</p>	<p style="text-align: right;">Page 112</p> <p>1 would like to make at this time?</p> <p>2 A Yes. I'd like to make one -- oh, yes.</p> <p>3 Well, page 72 in this version.</p> <p>4 MS. PARFITT: Just refer to the exhibit</p> <p>5 number, so 11.</p> <p>6 THE WITNESS: Exhibit 11, page 72,</p> <p>7 Table 2. Table 2 of the report.</p> <p>8 BY MS. BRANSCOME:</p> <p>9 Q What is the correction you would like to</p> <p>10 make?</p> <p>11 A The correction is -- there's a column</p> <p>12 called "Included in main meta-analysis," and I</p> <p>13 think in your copy, as in mine in this version,</p> <p>14 there are a bunch of question marks. In the</p> <p>15 original Word document that I submitted, these</p> <p>16 were not question marks. They were tick marks,</p> <p>17 checkmarks. And somehow in the translation of</p> <p>18 Word to PDF, this -- the tick mark -- the tick</p> <p>19 marks got changed to these funny little question</p> <p>20 marks. So they should all be tick marks.</p> <p>21 Q Are there any other corrections you</p> <p>22 would like to make to your report?</p> <p>23 A Not that I'm aware of at this time.</p> <p>24 Q Okay. So if you could turn to</p> <p>25 Exhibit 10 -- which is in front of you there -- if</p>
<p style="text-align: right;">Page 111</p> <p>1 A So the one outstanding one that we had</p> <p>2 highlighted -- or we've gone through the three of</p> <p>3 them.</p> <p>4 MS. PARFITT: 45.</p> <p>5 THE WITNESS: Have we --</p> <p>6 MS. PARFITT: No, 45. Page --</p> <p>7 MR. TISI: No, 47. 45.</p> <p>8 MS. PARFITT: Page 45. Excuse me, it's</p> <p>9 47.</p> <p>10 THE WITNESS: Oh, yes, that -- the</p> <p>11 question of whether that sentence should refer to</p> <p>12 Berge or Terry on that page. It's Berge 2018, not</p> <p>13 Terry. I was right the first time.</p> <p>14 MS. PARFITT: Oh, and it is page 45,</p> <p>15 just for the record. It is not 47. That was the</p> <p>16 first correction is on page 45.</p> <p>17 THE WITNESS: In this version.</p> <p>18 BY MS. BRANSCOME:</p> <p>19 Q So just to be clear, Dr. Siemiatycki, on</p> <p>20 the third line of page 45 of Exhibit 10, the</p> <p>21 reference to Terry 2013 in the sentence beginning</p> <p>22 with the word "while" should in fact be Berge</p> <p>23 2018?</p> <p>24 A Yes.</p> <p>25 Q Do you have any other corrections you</p>	<p style="text-align: right;">Page 113</p> <p>1 you could turn to your Conclusion section. It</p> <p>2 should be on page 69.</p> <p>3 A Yes.</p> <p>4 Q You state in the second paragraph below</p> <p>5 the Conclusion section that: "Based on the</p> <p>6 totality of the evidence, it is my opinion to a</p> <p>7 reasonable degree of scientific certainty that the</p> <p>8 perineal use of talcum powder products can cause</p> <p>9 ovarian cancer."</p> <p>10 First, did I read that correctly?</p> <p>11 A Yes, you did.</p> <p>12 Q Does that conclusion accurately</p> <p>13 summarize your opinion in this case as to whether</p> <p>14 or not perineal use of talcum powder can cause</p> <p>15 ovarian cancer?</p> <p>16 A Yes, it does.</p> <p>17 Q You state that your opinion is to a</p> <p>18 reasonable degree of scientific certainty,</p> <p>19 correct?</p> <p>20 A Correct.</p> <p>21 Q Is that a phrase that you have ever used</p> <p>22 in a scientific publication?</p> <p>23 A I don't think so.</p> <p>24 Q Why did you use it here?</p> <p>25 A I've seen this phrase used in all of the</p>

<p style="text-align: right;">Page 114</p> <p>1 expert opinions in the legal cases that I've seen, 2 and I inferred that it's a -- a formula that is 3 de rigueur in legal communications for this sort 4 of thing. 5 Q When you say "to a reasonable degree of 6 scientific certainty," what do you mean by that 7 phrase? 8 A So my -- you know, I think somewhere 9 else in the document, I -- I phrase it in a way 10 that I'm comfortable with, which is a way that 11 also is sort of derivative from my understanding 12 of legal jargon and precedence. I think that it's 13 more likely than not that there is a causal 14 relationship. 15 Q You anticipated where I was going with 16 my question. Do those two sentences mean anything 17 different to you? 18 A No. 19 Q What is your understanding of "more 20 likely than not"? 21 A From a strictly mathematical point of 22 view, it implies that I feel that there's greater 23 than 50 percent probability that this thesis is 24 true. And I wouldn't put a more quantitative 25 meaning onto it.</p>	<p style="text-align: right;">Page 116</p> <p>1 that exists today enable a scientist to parse that 2 out? 3 MS. PARFITT: Objection. Form. 4 THE WITNESS: I'm not sure I understand 5 the premise of the question, the "if" part. 6 BY MS. BRANSCOME: 7 Q Okay. So if the biological mechanism by 8 which a talcum powder product can cause ovarian 9 cancer is because of a particular contaminant in 10 that talcum powder product, but that contaminant 11 does not exist in all talcum powder products, 12 would the epidemiological evidence that exists 13 today allow you to see that distinction? 14 MS. PARFITT: Objection. Form. 15 THE WITNESS: The epidemiologic evidence 16 as -- as it exists today would not allow one to 17 parse out anything about the particular 18 manufacturer, the particular product, if I 19 understand your question correctly. 20 BY MS. BRANSCOME: 21 Q And so therefore, the epidemiological 22 evidence as it exists today does not have a level 23 of detail by which someone reviewing that data 24 could determine if there were different 25 contaminants present in different talcum powder</p>
<p style="text-align: right;">Page 115</p> <p>1 Q Is your opinion that perineal use of 2 talcum powder products can cause ovarian cancer, 3 is it specific to a single brand or manufacturer 4 of talcum powder? 5 A No, it isn't. 6 Q Why not? 7 A Because as I understand it, the 8 epidemiologic evidence that supports the thesis of 9 a causal relationship is derived from evidence 10 among women who used all types of talcum powder 11 products that were available in their consumer 12 area of purchase of these products. And whatever 13 was the frequency distribution of different 14 manufacturers and types of powdering that were 15 available in the consumer -- various consumer 16 markets were the types that lead to the overall 17 inference about causality, and there's no way for 18 me to parse out which particular manufacturer 19 would have been more or less responsible for any 20 of this. 21 Q If in fact, and we're just talking 22 hypothetically, the biological mechanism by which 23 some talcum powder products can cause ovarian 24 cancer is related to a contaminant in that talcum 25 powder product, does the epidemiological evidence</p>	<p style="text-align: right;">Page 117</p> <p>1 products that were used by individuals who 2 developed ovarian cancer -- 3 MS. PARFITT: Objection. Form. 4 BY MS. BRANSCOME: 5 Q -- correct? 6 MS. PARFITT: Objection. Form. 7 THE WITNESS: May I read the -- 8 MS. PARFITT: Yes, you can. 9 BY MS. BRANSCOME: 10 Q Of course. 11 A Just to make sure I understand. 12 (Peruses document.) 13 So I -- I don't think that the 14 epidemiological evidence would allow you to 15 attribute causality to a specific type or -- or 16 not. If one knew -- if part of your hypothetical 17 is the knowledge of what the constituents were of 18 different products used in different markets, and 19 the biological mechanism has been established to a 20 high degree of certainty, there might be some room 21 for making inferences about this. But that seems 22 like a tenuous possibility. 23 Q But you agree that the current 24 epidemiological evidence as it exists does not 25 enable someone to distinguish between brands of</p>

<p style="text-align: right;">Page 118</p> <p>1 cosmetic talc products, for example?  2 MS. PARFITT: Objection. Form.  3 THE WITNESS: I don't think it does.  4 BY MS. BRANSCOME:  5 Q Does -- is your opinion that perineal  6 use of talcum powder products can cause ovarian  7 cancer, is that limited to talcum powder products  8 manufactured during a certain time period?  9 A The evidence as it exists today pertains  10 to products manufactured over half a century,  11 roughly speaking, so I don't think that there's  12 any way to link it to products manufactured in a  13 particular time period.  14 In -- in answer to that question,  15 actually, and to the previous one, hypothetically,  16 one might imagine looking at the different  17 study -- the 30-odd studies that have been carried  18 out in different communities and different cities  19 and different countries, and if one could obtain  20 reliable, reasonably precise and time relevant  21 information on market shares of products in  22 different markets at different times, that could  23 give a first approximation of whether certain  24 company products are more closely linked to the  25 excesses that are seen in the epidemiological</p>	<p style="text-align: right;">Page 120</p> <p>1 ovarian cancer in that area, it would be  2 improbable that the product of that company were  3 not part of the responsibility, but one of the  4 companies that produced 5 or 10 percent of the  5 market share.  6 BY MS. BRANSCOME:  7 Q Okay. But as you sit here today, based  8 on the analysis that you have done, you are not  9 able to draw an opinion specifically about an  10 increased risk of ovarian cancer that is tied to a  11 particular brand or a particular time period,  12 correct?  13 MS. PARFITT: Objection. Form.  14 THE WITNESS: That's correct, in part  15 because I don't have data on market share at  16 different times and in different places.  17 BY MS. BRANSCOME:  18 Q Okay. In forming your opinion that  19 perineal talc use can cause ovarian cancer, did  20 you reach an opinion about how much talcum powder  21 is needed to cause ovarian cancer?  22 A No.  23 Q Is there an amount of talcum powder that  24 can be used perineally without increasing a risk  25 for ovarian cancer?</p>
<p style="text-align: right;">Page 119</p> <p>1 studies.  2 Q The application, though, of a market  3 share analysis to the users of talcum powder  4 products, if you're looking at causality, would  5 require that the individuals who developed ovarian  6 cancer had purchased their talcum powder according  7 to the market share, correct?  8 MS. PARFITT: Objection. Form.  9 THE WITNESS: Approximately, yes.  10 BY MS. BRANSCOME:  11 Q So, for example, if one type of talcum  12 powder product or one time period of talcum powder  13 product is the only type that actually causes  14 ovarian cancer, so all of the positives were  15 derived from those users, you -- you could not  16 determine that simply by applying market share,  17 for example?  18 MS. PARFITT: Objection. Form.  19 THE WITNESS: That -- that's true,  20 except in the circumstance that market share were  21 very, very high in most of the communities that  22 have been investigated. So if one company  23 produced 90 percent or 85 percent or something of  24 the product in a certain area -- that was consumed  25 in a certain area, and there's an excess risk of</p>	<p style="text-align: right;">Page 121</p> <p>1 A So let me go back to the previous  2 question, and clarify what do you mean by amount?  3 Do you mean like the amount in grams? The amount  4 in number of applications? The amount in number  5 of day -- days on which the powder is applied?  6 These are all different metrics of exposure, and  7 the answer might depend on what kind of -- you  8 know, we're starting with these studies. There  9 are now some hints about the dose-response  10 relationship and what kind of levels of exposure  11 in terms of number of applications in use,  12 observable excess risks.  13 Q So let me ask it this way: Did you  14 calculate how much talcum powder is needed to  15 cause ovarian cancer in any of the forms, be it  16 frequency of application, the amount in grams that  17 was used?  18 A I --  19 MS. PARFITT: Objection. Form.  20 THE WITNESS: I did not carry out such a  21 calculation. I'm -- my emphasis was on  22 determining whether there's a dose-response  23 relationship. Going beyond that might involve  24 trying to quantify the dose-response relationship  25 to the extent of determining what the shape of</p>

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1 such a relationship is and how the curve looks,  
2 whether there's a threshold effect, and so on.  
3 But I don't think there's enough data now to be  
4 able to make such estimates.  
5 BY MS. BRANSCOME:  
6 Q Can you rule out the possibility that  
7 there is a threshold below which perineal use of  
8 talc presents no risk of ovary -- of ovarian  
9 cancer?  
10 MS. PARFITT: Objection. Form.  
11 THE WITNESS: No, I -- I don't think --  
12 I can't, and I don't think it's possible to do  
13 that with most carcinogens. It's -- it's an  
14 extremely difficult and controversial issue of how  
15 to detect sort of a minimum level of exposure  
16 produces a carcinogenic effect.  
17 BY MS. BRANSCOME:  
18 Q In your view, has a dose-response  
19 relationship for the perineal application of talc  
20 and the development of ovarian cancer been  
21 established in the scientific literature?  
22 A My view is that the data are certainly  
23 compatible with the notion of a dose-response  
24 relationship. It -- it trends in that direction  
25 of that conclusion. It's not definitive yet.

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1 It's not definitive. But I believe the bulk of  
2 the evidence, especially from the Terry study and  
3 partly from, I think it's the, Schildkraut study,  
4 which are the most powerful ones for that  
5 question, but certainly the Terry study is by far  
6 the most important one, does tend to indicate  
7 dose-response relationship.  
8 Q Is the data that exists today also  
9 compatible with no dose-response relationship?  
10 MS. PARFITT: Objection. Form.  
11 THE WITNESS: Yes. It could be -- in  
12 other words, it could be a chance finding. Is --  
13 that's what you're saying. I think it's unlikely,  
14 but it's -- it can't be ruled out.  
15 BY MS. BRANSCOME:  
16 Q Are you offering an expert opinion that  
17 the inhalation of talc increases or presents any  
18 risk of ovarian cancer?  
19 A I -- I don't have an opinion on -- on  
20 that. No.  
21 Q Aside from your participation in the  
22 IARC panel in 2006 and the Langseth article on  
23 2008, has all of your work on talc and ovarian  
24 cancer been in connection with litigation?  
25 A On talc and -- sorry, work on talc and

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1 ovarian cancer, is that the question? Almost.  
2 But the one qualification I would make in  
3 answering that question is that I have a colleague  
4 who started working with -- in my academic  
5 department about 12 years ago, and she was  
6 interested in ovarian cancer as a topic of  
7 research, and she wanted to organize a case-  
8 control study of ovarian cancer in relation to  
9 various factors, and she asked me to kind of  
10 mentor her -- she was just starting out -- mentor  
11 her in getting grants, in setting up the study,  
12 and this sort of thing, and this is what I did  
13 with her.  
14 So I worked on grant applications with  
15 her on some aspects of setting up her study, and  
16 that has been going on now for -- I don't know --  
17 I think since 2010 maybe that she started. So --  
18 but that has not -- I've been what we call a  
19 coinvestigator on that project, not a principal  
20 investigator.  
21 But apart from that, the next stage in  
22 my involvement with talc and ovarian cancer was in  
23 the litigation.  
24 Q What is your colleague's name?  
25 A Anita Koushik.

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1 Q If you had to give me your best  
2 estimate, how many hours total have you spent  
3 assisting her with the case-control study?  
4 MS. PARFITT: Objection. Form,  
5 misstates his testimony.  
6 THE WITNESS: It's very hard to answer  
7 that. I mean, ten years ago discussions over  
8 coffee about studies and how to write grant  
9 applications and reviewing and revising and so on.  
10 I -- I don't -- not a trivial amount and not an  
11 overwhelming amount.  
12 BY MS. BRANSCOME:  
13 Q When was the last time that you spent  
14 hours in connection with that case-control study?  
15 MS. PARFITT: Objection. Form.  
16 THE WITNESS: There was a manuscript  
17 that came -- a publication that came from that  
18 study. It was -- the study was only completed in  
19 the field, the data collection, around two years  
20 ago, and spending a year cleaning data and so on,  
21 and then starting to analyze it.  
22 And there was an analysis of  
23 reproductive and hormonal factors in relation to  
24 ovarian cancer, and I helped her review and revise  
25 that manuscript. That would have been a year and

<p style="text-align: right;">Page 126</p> <p>1 a half ago or so, and I don't know, maybe I spent 2 three or four days on it at the time. 3 BY MS. BRANSCOME: 4 Q Did that study reach any conclusions 5 with respect to a potential link between perineal 6 use of talc and ovarian cancer? 7 A The talc information was collected in 8 the questionnaire and has not yet been analyzed. 9 Q Other than what we just discussed with 10 respect to the case-control study and then your 11 work in connection with the IARC panel and the 12 Langseth paper, have you ever done any original 13 research on the association between perineal 14 talcum powder use and ovarian cancer? 15 A No. No, I haven't. 16 It's common -- it's common for me to be 17 asked to review information on which I have not 18 directly worked. You know, topics. You know, I 19 recently was asked by the government of France to 20 evaluate a problem of possible cancer risks 21 related to a pesticide that's used in the banana 22 industry in Guadeloupe and Martinique. I've never 23 studied that pesticide and I've never been to 24 Martinique. But the kind of expertise that I have 25 can be applied to studying different sorts of</p>	<p style="text-align: right;">Page 128</p> <p>1 A That's correct. 2 Q Have you done anything since 2016 to 3 publicly announce your view that the perineal use 4 of talc can cause ovarian cancer? 5 A No, I've not had really an opportunity. 6 And in a way the -- the publication by Berge, 7 which appeared as a -- after I completed my 8 meta-analyses, and they -- they kind of beat me to 9 the punch with one type of publication output that 10 I might have produced. So I'm thinking about 11 different ways of communicating my results and my 12 opinions, but mainly my results. 13 I mean, the other part of the answer 14 to -- another part of the answer to your question 15 is that I'm not particularly a fan of individual 16 scientists going into press with opinions before 17 some sort of consensus starts to appear. I mean, 18 you can -- you can publish hypotheses and ideas, 19 but proclaiming conclusions is something that 20 should come later in the scientific process. I 21 mean, I -- I think it's best if IARC or an agency 22 like IARC would take on that role, and that would 23 be my hope actually. 24 Q In your opinion, has consensus formed 25 that peri- -- perineal use of talc can cause</p>
<p style="text-align: right;">Page 127</p> <p>1 problems. 2 Q You have not published the meta-analyses 3 that you -- meta-analysis you performed in 4 connection with the MDL, have you? 5 A No, I haven't. 6 Q Have you ever published in any peer- 7 reviewed article the opinion that the perineal use 8 of talcum powder can cause ovarian cancer? 9 A I -- I've never had occasion to opine 10 about this in any publication, and one doesn't 11 just announce to the New England Journal of 12 Medicine that you want to, you know, write an 13 article about opining about something like this. 14 There has to be some sort of platform basis of 15 research evaluation and so on. 16 And my involvement in this case might 17 lead to such a publication, but in the past I 18 would have not -- I had no reason to publish or to 19 try to publish such an opinion. 20 Q But you had formed an opinion with 21 respect to the perineal use of talcum powder and 22 an increased risk of ovarian cancer at the time 23 that you published your report in October of 2016. 24 And by "published," I mean within the 25 litigation context, correct?</p>	<p style="text-align: right;">Page 129</p> <p>1 ovarian cancer? 2 A I think among people who have reviewed 3 the evidence who -- sort of competent scientists 4 who have reviewed the evidence, I think there's 5 starting to be a ground swell of consensus about 6 it. You know, I've never done a survey, so I 7 can't say if it's majority or minority. 8 If your denominator is all medical 9 researchers, then the answer is, well, most of 10 them have never heard of this issue, so it's 11 not -- they wouldn't be susceptible to holding 12 such an opinion. But among the people who have 13 reviewed, are familiar with the issues, I think 14 there's certainly a much higher level of 15 receptivity to this thesis than there was ten 16 years ago. 17 Q Has a consensus been reached that 18 perineal use of talc probably causes ovarian 19 cancer? 20 MS. PARFITT: Objection. Asked and 21 answered. Form. 22 THE WITNESS: I can't answer that 23 question. I -- it's too -- are you trying to make 24 the distinction between probably and -- I -- so -- 25 BY MS. BRANSCOME:</p>

<p style="text-align: right;">Page 130</p> <p>1 Q Well, what do you understand the phrase</p> <p>2 "can cause ovarian cancer" to mean?</p> <p>3 A Well, it's a synonym with "is a risk</p> <p>4 factor for" or -- that's how I understand it.</p> <p>5 Q All right. And is that in your mind the</p> <p>6 same as "it probably causes cancer"?</p> <p>7 MS. PARFITT: Objection. Form.</p> <p>8 THE WITNESS: "It probably can cause,"</p> <p>9 is that what you said, or "probably does cause"?</p> <p>10 BY MS. BRANSCOME:</p> <p>11 Q Probably does cause.</p> <p>12 A So I don't think any risk factor can be</p> <p>13 described as -- in a way with the wording "does</p> <p>14 cause." You know, smoking does not cause lung</p> <p>15 cancer. It can cause lung cancer when there's a</p> <p>16 constellation of other favorable circumstances.</p> <p>17 You know, this is part of multifactorial causation</p> <p>18 of disease. So, you know, each factor in itself</p> <p>19 is not the cause, but it's part of a constellation</p> <p>20 of factors that together can cause the disease.</p> <p>21 So each of them can cause the disease.</p> <p>22 Q So -- you -- you state in your report</p> <p>23 that -- let me see if I can get the exact</p> <p>24 language.</p> <p>25 And perhaps you can get me there more</p>	<p style="text-align: right;">Page 132</p> <p>1 THE WITNESS: I don't know -- I haven't</p> <p>2 carried out a survey among people. I don't know</p> <p>3 whether a consensus has been reached. I don't</p> <p>4 know what proportion of that community would</p> <p>5 subscribe to this point of view or not.</p> <p>6 BY MS. BRANSCOME:</p> <p>7 Q Okay. Setting aside conducting a survey</p> <p>8 of individuals in the scientific community, would</p> <p>9 you say that the scientific literature reflects a</p> <p>10 consensus that the causal relationship between</p> <p>11 perineal talc powder exposure and ovarian cancer</p> <p>12 is probable?</p> <p>13 MS. PARFITT: Objection. Form.</p> <p>14 THE WITNESS: I think the scientific</p> <p>15 literature supports that conclusion. I'm not sure</p> <p>16 that it reflects it.</p> <p>17 So there's kind of a lag period between</p> <p>18 the production of research findings and the</p> <p>19 consensus -- a consensus building around it and</p> <p>20 being expressed in print. You know, if we take</p> <p>21 sort of the classic smoking and lung cancer</p> <p>22 historical example, evidence was accumulating</p> <p>23 rapidly in the 1950s. There were several studies</p> <p>24 through the 1950s and early 1960s, and it was only</p> <p>25 in 1964, so many years after some of this evidence</p>
<p style="text-align: right;">Page 131</p> <p>1 quickly. You talk about that now you would give a</p> <p>2 different rating under the IARC standard.</p> <p>3 Ah, here we go. Page 67 in your 2018</p> <p>4 report. You state: "It is now my professional</p> <p>5 opinion based on the totality of the evidence,</p> <p>6 that to a reasonable degree of scientific</p> <p>7 certainty, the causal relationship between</p> <p>8 perineal talc powder exposure and ovarian cancer</p> <p>9 is," quote, "probable."</p> <p>10 Did I read that correctly?</p> <p>11 A You did.</p> <p>12 Q Do you hold that opinion?</p> <p>13 A Yes, I do.</p> <p>14 Q What do you mean when you say a "causal</p> <p>15 relationship between perineal talc powder exposure</p> <p>16 and ovarian cancer is," quote, "probable"?</p> <p>17 A I mean it's more likely than not.</p> <p>18 Q Okay. Has a consensus been reached in</p> <p>19 the scientific community, understanding we're</p> <p>20 looking at those who have an interest in this</p> <p>21 issue, been reached that the causal relationship</p> <p>22 between perineal talc powder and ovarian cancer is</p> <p>23 probable?</p> <p>24 MS. PARFITT: Objection. Form, asked</p> <p>25 and answered.</p>	<p style="text-align: right;">Page 133</p> <p>1 had been published and been accepted by many</p> <p>2 scientists, but rejected by others -- there was</p> <p>3 still controversy around it -- that the Surgeon</p> <p>4 General's report reflected and created a</p> <p>5 consensus.</p> <p>6 BY MS. BRANSCOME:</p> <p>7 Q So in early 2019, are we still in the</p> <p>8 lag period or the period in which the production</p> <p>9 of research findings is still behind consensus</p> <p>10 building in the literature?</p> <p>11 MS. PARFITT: Objection. Form,</p> <p>12 misstates his testimony.</p> <p>13 THE WITNESS: Does that mean I should</p> <p>14 answer or --</p> <p>15 MS. PARFITT: I'm objecting. I said it</p> <p>16 misstates your prior testimony.</p> <p>17 THE WITNESS: Okay. Sorry. Let me read</p> <p>18 the question again. (Peruses monitor.)</p> <p>19 So I can't point to hallmark</p> <p>20 publications analogous to the Surgeon General's</p> <p>21 report for smoking and lung cancer that would</p> <p>22 reflect such a bend in the road kind of general</p> <p>23 perception of the talc ovarian cancer issue. It</p> <p>24 doesn't mean that the evidence isn't there, but</p> <p>25 the process of recognizing and generalizing and so</p>

<p style="text-align: right;">Page 134</p> <p>1 on is not -- has not been achieved yet.</p> <p>2 BY MS. BRANSCOME:</p> <p>3 Q Okay. Have you ever given a lecture,</p> <p>4 either to students or to other scientists, in</p> <p>5 which you have presented your view that the</p> <p>6 perineal use of talcum powder can cause ovarian</p> <p>7 cancer?</p> <p>8 A I have to my students -- I mean to the</p> <p>9 students in my department. I teach epidemiologic</p> <p>10 methods. I don't teach about ovarian cancer. I</p> <p>11 don't teach about talc. That's not what I'm paid</p> <p>12 to do. I'm paid to teach about the methodology</p> <p>13 and the conduct of -- and the interpretation of</p> <p>14 epidemiologic -- and I've used the talc/ovarian</p> <p>15 cancer as an example and walked my students</p> <p>16 through the evidence. So, yes, I have.</p> <p>17 Q When did you start teaching that as part</p> <p>18 of your epidemiological methods course?</p> <p>19 A Probably two years ago. As soon as I</p> <p>20 started gathering the information and synthesizing</p> <p>21 it, so two -- two or three years ago.</p> <p>22 Q Other than presenting to your students</p> <p>23 your analysis of talc and ovarian cancer as an</p> <p>24 illustration of an epidemiological method, have</p> <p>25 you presented your opinion that perineal use of</p>	<p style="text-align: right;">Page 136</p> <p>1 think. (Peruses document.)</p> <p>2 Q Okay.</p> <p>3 A No, I've never spoken to any of them</p> <p>4 about -- I -- I crossed paths with Dr. Cramer in</p> <p>5 Los Angeles for a -- you know, we were in the same</p> <p>6 hotel. He was leaving, I was coming, that sort of</p> <p>7 thing, but I don't think we had any substantive</p> <p>8 discussion, and I can't -- I know some of the</p> <p>9 others, but I've never spoken to them about this</p> <p>10 issue.</p> <p>11 Q Do you know personally or professionally</p> <p>12 any of the other plaintiffs' experts in the MDL?</p> <p>13 A No, I don't.</p> <p>14 Q You were chair of the working group --</p> <p>15 the IARC Working Group that published the</p> <p>16 monograph on talc in 2006 -- or, well, that met in</p> <p>17 2006, and then was subsequently published in 2010,</p> <p>18 correct?</p> <p>19 A That's correct.</p> <p>20 Q And there were roughly 20 members of</p> <p>21 that working group?</p> <p>22 A I think so.</p> <p>23 Q In 2006, you agreed with the IARC</p> <p>24 classification of, quote, "possible" describing</p> <p>25 the relationship between perineal talc use and</p>
<p style="text-align: right;">Page 135</p> <p>1 talcum powder can cause ovarian cancer in any</p> <p>2 other context outside of litigation?</p> <p>3 A No, I haven't.</p> <p>4 Q Have you spoken with other scientists</p> <p>5 about the issue of whether perineal use of talcum</p> <p>6 powder can cause ovarian cancer? Setting aside</p> <p>7 your students.</p> <p>8 A Yeah. Yes, I've spoken to -- to</p> <p>9 colleagues, friends over -- over coffee, over</p> <p>10 drinks at conferences, you know, what are you up</p> <p>11 to, what are you doing, and then describe my</p> <p>12 involvement in this case. And then we dig a</p> <p>13 little further into, Well, what -- what do you</p> <p>14 think, and so on. So I -- I have discussed it in</p> <p>15 that kind of format.</p> <p>16 Q Have you ever spoken with any of the</p> <p>17 authors on any of the papers that you cite in your</p> <p>18 report about the potential link between perineal</p> <p>19 use of talc and ovarian cancer?</p> <p>20 A I don't think so. I can quickly scroll</p> <p>21 through the list to see if anything jogs my --</p> <p>22 yeah -- no, let me --</p> <p>23 Q If you can do that quickly, we could do</p> <p>24 it now, or we can save that for the next break.</p> <p>25 A It will take just three minutes, I</p>	<p style="text-align: right;">Page 137</p> <p>1 ovarian cancer, correct?</p> <p>2 MS. PARFITT: Objection. Form.</p> <p>3 THE WITNESS: That's correct. I could</p> <p>4 read the exact wording of what "to be" means, but</p> <p>5 that's the gist of it.</p> <p>6 BY MS. BRANSCOME:</p> <p>7 Q Okay. IARC has not changed its</p> <p>8 clarification of talc, and specifically with</p> <p>9 respect to the peri- -- perineal use of talc since</p> <p>10 it published the 2010 monograph, correct?</p> <p>11 A Technically correct, but actually,</p> <p>12 what -- the correct statement is IARC has not</p> <p>13 evaluated talc since 2006 -- has not reevaluated.</p> <p>14 So there are no changes made to IARC evaluations</p> <p>15 except through a formal complete reevaluation, and</p> <p>16 there has not been a formal complete reevaluation</p> <p>17 of talc since the 2006 meeting. So there's no</p> <p>18 opportunity for IARC to change anything in one</p> <p>19 direction or another failing another complete</p> <p>20 evaluation.</p> <p>21 Q What, if you know, can initiate a formal</p> <p>22 complete evaluation of a constituent like talc?</p> <p>23 A Well, it comes I think from different</p> <p>24 sources. I'm not entirely certain. I know that</p> <p>25 there is now a public process whereby public</p>

<p style="text-align: right;">Page 138</p> <p>1 parties can write to the monograph program and  2 make suggestions for chemicals to be evaluated.  3 There are -- they get requests from governments.  4 They get requests from groups of scientists. They  5 have their own internal scientific staff that has  6 its antenna out for different problems that arise,  7 and they generally have sort of a five-year  8 program of agents that they are going to evaluate  9 in every -- in the next five-year period.  10 These things are not quick and easy to  11 organize, and so there's a lot of lead time.  12 There's a lot of, in a way, competition for agents  13 to get onto the list to be evaluated. There are a  14 lot of interested parties that would like the  15 agent that they are exposed to or the "et cetera"  16 to be evaluated. So the exact mechanics of how  17 they make decisions, I haven't been involved in  18 that process, but that's, roughly speaking, how  19 it's done.  20 Q Have you ever submitted a request to  21 IARC for them to conduct a complete evaluation of  22 talc?  23 A Have I ever?  24 Q Have you since the publication of the  25 monograph in 2010 submitted a request to IARC for</p>	<p style="text-align: right;">Page 140</p> <p>1 sentence -- you know, in the context of a  2 conversation about many things, as we do when we  3 catch up when we meet. What -- you know, what's  4 on the agenda for the monograph program? By the  5 way, I think talc might be an interesting thing to  6 put on a list for you to consider. And probably  7 the conversation ended -- that part of the  8 conversation ended and moved on to other things.  9 But...  10 MR. KLATT: Should we take a break?  11 MS. BRANSCOME: I understand the noise,  12 but I -- I don't know that Dr. Siemiatycki was  13 finished with his answer.  14 MS. PARFITT: We'll keep going. I  15 didn't -- I was trying to keep a clean record for  16 you. That's fine. Keep going.  17 MS. BRANSCOME: Well, we -- we can  18 pause. I just was trying to let him finish his  19 answer.  20 MS. PARFITT: We'll keep it paused here  21 on the screen. Just a little bit more activity.  22 THE VIDEOGRAPHER: We will pause for a  23 second. We're going off the record, 2:41 a.m. --  24 p.m.  25 (Pause.)</p>
<p style="text-align: right;">Page 139</p> <p>1 them to conduct another complete evaluation of  2 talc?  3 A I had a quick word with the director of  4 the monograph program a few months ago, and I  5 suggested it might be time for that. But I'm  6 intending to submit a more formal request along  7 those lines. So...  8 Q Okay. Who -- who specifically did you  9 speak with a few months ago?  10 A The director of the monograph program is  11 Kurt Straif, S-T-R-A-I-F.  12 Q And how did you have occasion to be  13 speaking with the director?  14 A We're acquaintances, and I met him at a  15 conference in August, I saw him when I was in Lyon  16 in November at a meeting that he organized. So  17 I've seen him a few times in the last six months.  18 Q When did you have this conversation with  19 the director?  20 A I think it was in the summer.  21 Q So the summer of 2018?  22 A Yeah.  23 Q And what specifically did you discuss  24 with him?  25 A I -- I think it might have been a one</p>	<p style="text-align: right;">Page 141</p> <p>1 THE VIDEOGRAPHER: We're going back on  2 the record at 2:43 p.m.  3 BY MS. BRANSCOME:  4 Q When you spoke with the director of the  5 monograph program for IARC last summer, did you  6 inform him that you have been serving as an expert  7 witness on behalf of plaintiffs in litigation  8 involving talcum powder products and the claim  9 that they cause ovarian cancer?  10 A I'm not sure if I told him at that time,  11 but I certainly have told him since then.  12 Q When you were talking to him about the  13 possibility of including talc in a formal,  14 complete evaluation subsequent to the one that was  15 done in 2006 and published in 2010, did you tell  16 him anything about your opinions with respect to  17 the likelihood that perineal use of talc can cause  18 ovarian cancer?  19 A I don't think I did.  20 Q What did he say about -- if anything,  21 about conducting a formal evaluation of talc?  22 A I -- I can't remember if he said  23 anything about it.  24 Q Have you had any conversations with him  25 other than the conversation you had last summer</p>

<p style="text-align: right;">Page 142</p> <p>1 about IARC conducting another examination of talc  2 and its potential carcino- -- carcinogenicity --  3 whoops, butchered that one -- about it's ability  4 to cause cancer?  5 A No. I don't think I did.  6 Q Now, you said you have an -- you have  7 the intention to submit something formal to IARC;  8 is that correct?  9 A Yes. I've been thinking about it, and  10 I -- when I have time, I'll look into the process.  11 Q What specifically would you request that  12 IARC do at this time with respect to talc?  13 A Carry out an evaluation like they did in  14 2006 but with up-to-date data.  15 Q What data specifically do you think an  16 IARC Working Group would need to consider that was  17 not available in 2006? What are the key pieces of  18 data that you think should be considered by a  19 working group?  20 A So from an epidemiological database  21 point of view, there have been a number of  22 publications, as you know, since 2006, including  23 some cohort studies, various case-control studies,  24 various meta-analyses, a pooled analysis from the  25 Terry group. All of that information bears on the</p>	<p style="text-align: right;">Page 144</p> <p>1 sufficient growth in the information base that  2 would justify it. And the question is whether  3 there are other priorities -- that they have  4 things with even higher priorities for them to  5 look at.  6 Q We agree the perineal use of talc  7 currently is classified by IARC as a Group 2B  8 chemical, correct?  9 A Correct.  10 Q So the classification or the definition  11 of a Group 2A chemical still applies when there is  12 limited evidence of carcinogenicity in humans and  13 then sufficient evidence of carcinogenicity in  14 experimental animals, correct?  15 A Yes.  16 Q Has there been developments in the  17 experimental animal data since the IARC Working  18 Group evaluated the risks associated with the  19 perineal use of talc in 2006?  20 A I'm not aware whether there has been.  21 I -- it does not spring to mind. I can't think of  22 any examples.  23 Q Now, I noticed in your report you have a  24 description, it's on page 24, of the different  25 categories that IARC might rate a chemical.</p>
<p style="text-align: right;">Page 143</p> <p>1 evaluation of cancer risk. It -- it may or may  2 not change the view of a working group vis-à-vis  3 the view held by the 2006 working group, but  4 there's enough new information there that it could  5 potentially change points of view.  6 And in the mechanism area, I understand  7 that there has been additional work on various  8 possible areas of -- concerning the migration of  9 particles around the body and how this might  10 influence the -- the biological plausibility of  11 such a -- a process. The possible role, roles of  12 inflammation or oxidative stress. There have been  13 developments -- there are new publications in  14 those areas that might influence a new working  15 group or a working group looking at it with new  16 eyes.  17 For all of those reasons, I think it  18 would be timely, and in any case, if a decision  19 were made today to do this, such a meeting would  20 probably not be held before 2022 or 2023 at the  21 earliest. They have a horizon of priorities that  22 they're working on. So -- and by then, there  23 would likely be additional work that would be  24 available.  25 So it's an area where I think there is</p>	<p style="text-align: right;">Page 145</p> <p>1 Do you see where I am?  2 A Yes, I see where you are.  3 Q Okay. And there's a rating system that  4 IARC uses that ranges from 1 to 4, correct?  5 A Yes.  6 Q That -- you have indicated here on  7 page 24 on your report that number 4 is not a  8 carcinogen. Is that accurate? Is that an  9 accurate description of category 4?  10 A The wording is longer than that, but  11 this is my potted version of what that longer  12 version means.  13 Q The actual definition is that it is  14 probably not carcinogenic, correct?  15 A Correct.  16 MS. BRANSCOME: Would now be a good time  17 for a break?  18 MS. PARFITT: I think so. We can take a  19 break. Thank you.  20 THE VIDEOGRAPHER: We are going off the  21 record at 2:51 p.m.  22 (Recess.)  23 THE VIDEOGRAPHER: This is the beginning  24 disc number 4 in the deposition of Jack  25 Siemiatycki. We're going back on the record at</p>

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1 3:27 p.m.  
 2 BY MS. BRANSCOME:  
 3 Q Good afternoon, again, Dr. Siemiatycki.  
 4 A Hi.  
 5 Q Do you still agree with the IARC  
 6 characterization that the case-control studies  
 7 evaluating a potential connection between perineal  
 8 talc powder exposure and ovarian cancer are  
 9 unusually consistent?  
 10 A Unusually -- they're very consistent.  
 11 I'm not sure I would choose the word "unusually."  
 12 Sometimes when 20 people write a document,  
 13 everyone doesn't agree with every word, but they  
 14 are very consistent.  
 15 Q Do you agree with the IARC determination  
 16 that the excess in risk in those case-control  
 17 studies is, quote, modest?  
 18 A That the what, the increase in risk?  
 19 Q Or the excess of risk.  
 20 A Yeah, the -- I mean, the terminology  
 21 around strength of association -- weak, modest,  
 22 strong, very strong, medium, et cetera -- it  
 23 doesn't have -- there are no regulations. There's  
 24 no epidemiologic handbook that says if a relative  
 25 risk is in this range, you call it weak or

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1 moderate and so on and so forth.  
 2 So the term "moderate" -- actually, the  
 3 terminology around strength of associations was  
 4 probably most influenced by the smoking and lung  
 5 cancer situation in the '50s and '60s where there  
 6 were relative risks of ten approximately, ten  
 7 times as high of risk for smokers as for  
 8 nonsmokers of getting lung cancer, and that was  
 9 considered a benchmark for strong associations.  
 10 And it was not known then whether most carcinogens  
 11 would fall -- most carcinogens that would be  
 12 discovered later than that era would fall into the  
 13 category, you know, of relative risks, around ten  
 14 or around five or around two or whatever.  
 15 So the -- the use of the terms "strong,"  
 16 "medium," "weak" has kind of been -- what's the  
 17 word? -- benchmarked, I guess, by the smoking-lung  
 18 cancer association. And things that --  
 19 subsequently relative risks that were less than in  
 20 that order of magnitude of ten or so where people  
 21 didn't refer to them as strong because they were  
 22 not as strong as smoking and lung cancer.  
 23 It has subsequently turned out that the  
 24 level of relative risk for smoking and lung cancer  
 25 is exceptional among known carcinogens, and that

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1 this -- there are not many that have such high  
 2 relative risks.  
 3 I'm just giving you a bit of background  
 4 because the terminology is controversial, and I  
 5 know it plays into the case of how we -- how we  
 6 characterize the associations around talc and  
 7 ovarian cancer.  
 8 There are a lot of associations that are  
 9 much less than -- with relative risks much lower  
 10 than ten that are very well accepted as being  
 11 causal associations. And so the idea that  
 12 associations have to be, quote/un- -- quote,  
 13 strong in the sense that the smoking-lung cancer  
 14 association was strong is not really tenable any  
 15 more. There are so many -- most known carcinogens  
 16 don't have such strong -- don't have such high  
 17 relative risks. So where you draw the line  
 18 between strong, moderate, weak, and so on, is a  
 19 kind of -- is a vague notion.  
 20 If you're asking me how I would  
 21 characterize it or how it's characterized -- I'm  
 22 not sure whether you want to go -- to ask how I  
 23 would characterize it or how it's characterized by  
 24 other people or --  
 25 Q So, respectfully, Dr. Siemiatycki, my

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1 question was, do you agree with the IARC  
 2 classification of the increase in risk as, quote,  
 3 modest?  
 4 A So there was no such classification. It  
 5 was a word used in a sentence, I guess. There  
 6 is -- they never classified the association as  
 7 being strong, weak, moderate or whatever. It was  
 8 part of a narrative about the -- the body of  
 9 evidence.  
 10 Do I agree that -- yeah, I would use  
 11 that term today.  
 12 I'm sorry if I digressed from your  
 13 question.  
 14 Q You would agree that the point estimate  
 15 of the meta-analysis that you conducted in 2018  
 16 that's contained in your report marked Exhibit 10  
 17 is actually lower than the point estimate that was  
 18 reported in the Langseth 2008 study, correct?  
 19 A That's correct.  
 20 Q And the Langseth 2008 paper, the  
 21 meta-analysis that you and your coauthors  
 22 conducted resulted in a 1.35 relative risk,  
 23 correct?  
 24 A That's correct.  
 25 Q And in Exhibit 10, your report in the

<p style="text-align: right;">Page 150</p> <p>1 MDL, the relative risk point for your 2018 2 meta-analysis is 1.28, correct? 3 A In the 2018 -- yes, that's correct. 4 Q Is it your opinion -- well, let me just 5 ask you, what classification should perineal use 6 of talc get with respect to ovarian cancer under 7 the IARC scale? 8 MS. PARFITT: Objection. Form. 9 THE WITNESS: I -- I'm very reluctant to 10 answer that question because it takes a lot of 11 input from different disciplines to produce an 12 IARC evaluation and then IARC classification. And 13 I feel it's presumptuous for any one person from 14 one discipline to take on that function. 15 What I can say is that in this 16 situation, the epidemiologic evidence alone is 17 sufficient to make the -- make me think that it's 18 more likely than not that there is a causal 19 association. How that proposition would feed into 20 an IARC evaluation is something that would -- that 21 a multidisciplinary group would need to work out, 22 but I think there's at least enough evidence to 23 say it's more likely than not. 24 BY MS. BRANSCOME: 25 Q Because you would agree that a work --</p>	<p style="text-align: right;">Page 152</p> <p>1 causality, but it's not a one-to-one kind of 2 relationship. 3 Now I've lost the thread. I'm sorry. 4 BY MS. BRANSCOME: 5 Q That's okay. I'm going to ask you the 6 question again. 7 Simply the fact that the epidemiological 8 evidence -- 9 A Yeah. 10 Q -- may support a conclusion that more 11 likely than not perineal talc use can cause 12 ovarian cancer, that fact alone is not sufficient 13 to result in a Group 2A classification of a 14 chemical under IARC. 15 MS. PARFITT: Objection. Form. 16 BY MS. BRANSCOME: 17 Q Is that fair? 18 A It's fair -- in principle, it's a fair 19 statement. My feeling is that if that occurred in 20 a meeting, and if -- you know, in an IARC Working 21 Group, the group is subdivided into four 22 subgroups: Initially, an epidemiology group, 23 animal experimentation group, other biological 24 mechanisms, and then expose -- an exposure group. 25 If the epidemiology group came back, had</p>
<p style="text-align: right;">Page 151</p> <p>1 an IARC Working Group, for example, if a former -- 2 formal evaluation was done on talc, in order to 3 classify talc as say a Group 2A, that working 4 group would need to consider multiple lines of 5 evidence, correct? 6 MS. PARFITT: Objection. Form. 7 THE WITNESS: That's correct. 8 BY MS. BRANSCOME: 9 Q And simply the determination, if it were 10 the case that the epidemiological evidence might 11 support the conclusion that perineal use of talc 12 more likely than not can cause ovarian cancer, 13 would not by itself be sufficient for a Group 2A 14 rating. Is that fair? 15 MS. PARFITT: Objection. Form. 16 THE WITNESS: The IARC classification 17 was developed in the 1970s. It was not developed 18 in order to fit into a template that can be used 19 in the courtroom. So terms like "more likely than 20 not" or, you know, whatever terminology would be 21 used in a courtroom around this sort of thing does 22 not fit perfectly on the IARC classification 23 scale. 24 I understand why courts use IARC 25 evaluations as an input to understanding</p>	<p style="text-align: right;">Page 153</p> <p>1 a feeling that there likely -- it was more likely 2 than not that there is a causal association, they 3 have the prerogative to categorize the evidence as 4 being sufficient or limited. And it's not clear 5 how they would categorize the epidemiologic 6 evidence. That would feed into the final 7 evaluation. 8 Q So you would say, as you sit here today, 9 based on what you know about the epidemiological 10 evidence with respect to the perineal use of talc 11 and ovarian cancer, it's not clear whether that 12 would satisfy the criteria for sufficient evidence 13 of carcinogenicity. Is that fair? 14 MS. PARFITT: Objection. Misstates his 15 testimony. 16 THE WITNESS: For -- for a particular 17 working group. Because the other particularity of 18 the IARC process, as with other -- from high level 19 scientific processes, is that it depends a lot on 20 scientific judgment. There's -- there are 21 guidelines for how to combine animal evidence and 22 basic biology evidence in epidemiology, but all of 23 these guidelines are just models of how the final 24 evaluation might be determined. 25 Each working group is sovereign and can</p>

<p style="text-align: right;">Page 154</p> <p>1 take the entire body of evidence and make a 2 decision outside the -- the template -- the -- the 3 typical template. So a working group could look 4 at the evidence and decide is it Group 1, it's 5 Group 2B, Group 2A, based on the totality of 6 evidence. 7 In general, if the epidemiology is 8 convincing, it would be Group 1 or Group 2A if 9 it's convincing but not -- or let's say if it's -- 10 if it indicates a risk but it's not definitive. 11 BY MS. BRANSCOME: 12 Q So you would say if the epidemiology 13 indicates a risk but is not definitive, you think 14 there's a possibility a chemical would be 15 classified as Group 1? 16 MS. PARFITT: Objection. Form. 17 THE WITNESS: It depends how close to 18 definitive it is. So if the feeling of the group 19 is that it's almost certain on the basis of 20 epidemiologic evidence, then they could classify 21 it as Group 1, and they would classify the 22 epidemiologic evidence as sufficient in that case. 23 BY MS. BRANSCOME: 24 Q Okay. On the scale of definitiveness, 25 where would you place the evidence of the perineal</p>	<p style="text-align: right;">Page 156</p> <p>1 (A discussion was held off the record.) 2 BY MS. BRANSCOME: 3 Q Do you remember what you were answering 4 or should we -- 5 A I prefer if -- I'm sorry. If you could 6 ask again and -- 7 Q Let me ask it a different way. Is it 8 possible for a confounding variable to essentially 9 infect all of the epidemiology on a particular -- 10 looking at a particular causal relationship? 11 MS. PARFITT: Objection. Form. 12 THE WITNESS: It is possible. 13 BY MS. BRANSCOME: 14 Q Okay. If that were to happen and you 15 see evidence in the epidemiology that shows a 16 consistent increase in risk but there's the 17 potential for a confounding variable, would it be 18 important to look at the potential biological 19 mechanism to see whether or not the agent might be 20 causing the outcome? 21 A So the confounding factor is -- is a 22 factor that could be captured in epidemiologic 23 studies but hasn't been. Is that what you are 24 alluding to? And the biologic -- but the biologic 25 mechanism that you're referring to would involve</p>
<p style="text-align: right;">Page 155</p> <p>1 use of talc and ovarian cancer as of today? 2 A Based on the epidemiologic evidence. 3 Q Correct. 4 A I -- I go back to more likely than not. 5 Not -- not definite, but more likely than not. 6 Q Is it possible to have a situation where 7 the epidemiological evidence is supportive of a 8 causal association, but the group working on 9 biological mechanism determines that there isn't a 10 sufficient mechanism by which that chemical could 11 have caused that outcome? 12 A That can happen. 13 Q And what would the explanation for an 14 inconsistency like that be? 15 A It would require quite a high level of 16 understanding of the mechanistic evidence. 17 So -- I -- I don't know if it has 18 happened, so I'm -- I'm trying to think through 19 memory whether I can think of any examples. I'm 20 not sure that it has happened. 21 THE VIDEOGRAPHER: Excuse me, Counsel. 22 The microphone just fell. 23 THE WITNESS: Oh, I'm sorry. 24 MS. BRANSCOME: That's okay. You just 25 knocked off your microphone.</p>	<p style="text-align: right;">Page 157</p> <p>1 that confounding factor or is this -- are you -- 2 are you confounding "confounding" with -- with 3 biologic mechanism issues? 4 Q Okay. Let me -- let me give you a 5 specific hypothetical. 6 A Yes. 7 Q Okay. So let's say hypothetically, for 8 example, recall bias -- 9 A Okay. 10 Q -- affects the epidemiology related to 11 looking at the causal relationship, and whether 12 you agree with it or not, but we'll just say 13 hypothetically that affected the epidemiology of 14 talc use and ovarian cancer. 15 A Can I just interrupt for a 16 terminological thing? So typically we don't refer 17 to recall bias as a confounding factor. 18 Q Ah. 19 A We refer to it as a bias, a type of 20 bias, but -- you know, that's just technical, but 21 for the record, if we're going to be discussing 22 this further. 23 Q I appreciate the clarification. 24 A Thank you. 25 Q Well, first of all, let me just ask you,</p>

<p style="text-align: right;">Page 158</p> <p>1 is recall bias something that could affect the 2 reliability of conclusions drawn from 3 epidemiological studies that rely on recall to 4 define exposure to the agent? 5 A Yes, it could, hypothetically. 6 Q Okay. Is recall bias something that 7 potentially could affect the epidemiological 8 studies of the perineal use of talc? 9 A Yes, theoretically, it could. 10 Q Okay. In situations where there is a 11 potential bias or a confounding variable that has 12 not been identified, how should epidemiological 13 evidence be evaluated in comparison to the other 14 categories of evidence that are considered, for 15 example, by an IARC Working Group? 16 A Well, these things would typically be 17 evaluated in a -- a nonquantitative way. You 18 can't really quantify what is the potential impact 19 of a confounder that you don't know about or that 20 you haven't measured. It's kind of a theoretical 21 thing. 22 And the same with -- with recall bias 23 where there could be some evidence about it. And 24 certainly when I reviewed the evidence on this 25 topic, the possibility of recall bias was one of</p>	<p style="text-align: right;">Page 160</p> <p>1 exposures, all -- you know, environmental things 2 that they've been exposed to, et cetera, there -- 3 there's no reason why exposure to talc would be 4 the one item in epidemiologic questionnaires that 5 would provoke recall bias where nothing else does. 6 So if it's a part of a general 7 phenomenon, this recall bias, which is certainly a 8 hypothetical possibility, we would see that most 9 of the associations that were tested in case- 10 control studies would be found to be high risks, 11 maybe significantly high risks. 12 That's not what we observed. That's not 13 what I've observed in my research. I have 14 estimated -- and in the book that I showed this 15 morning, there are literally thousands of odds 16 ratio estimates in there. But in all of my 17 research on over nearly four decades, I've 18 published a lot of evidence, and I can show some 19 examples, where there's no difference between 20 cases and controls because there is no effect, 21 there's no causal association between the two 22 things, and the case -- although people were -- 23 cases were asked about, let's say, alcohol 24 consumption, and controls were asked about alcohol 25 consumptions, the cases didn't overreport. They</p>
<p style="text-align: right;">Page 159</p> <p>1 the main stumbling blocks to arriving at an 2 opinion, as it was for the IARC panel in 2006. 3 You know, we are all aware of that hypothetical 4 possibility, and we think about whether something 5 of that magnitude -- something like that could 6 artifactually generate an appearance of a relative 7 risk. 8 My own way of dealing with that was to 9 look at the phenomenon of recall bias from the 10 perspective of both my own research, which has 11 mainly involved case-control studies, some cohort 12 studies but mainly case-control studies, and 13 research that I've read about, experienced, 14 reviewed for journals, et cetera. 15 And if the phenomenon of recall bias 16 were sort of a general across-the-board phenomenon 17 that infects and in a way discredits all 18 case-control studies -- interviewing cases, people 19 who are sick people, interviewing people who are 20 well and comparing the responses -- if this were 21 an inherent systemic problem, what we would 22 observe in general would be a plethora of fake 23 excess risks. Because almost everything you would 24 ask people about, whether it's smoking, alcohol 25 consumption, physical activity, diet, workplace</p>	<p style="text-align: right;">Page 161</p> <p>1 didn't say, Oh, well, they want to know if this 2 caused my cancer, and therefore I'm going to tell 3 them, yes, I consumed a lot of beer and wine and 4 so on, or smoking or whatever. 5 So we don't see this as a general 6 phenomenon that people overreport -- that cases 7 overreport compared to controls. 8 Q Have you looked at the phenomenon of 9 recall bias specifically when the agent being 10 investigated is part of public wide -- wide scale 11 litigation? 12 MS. PARFITT: Object to form. 13 THE WITNESS: So I haven't personally -- 14 let me just think if any of my research has 15 involved situations analogous to that. 16 Yes. Cell phones and brain cancer. So 17 I was involved in a large cell phone and brain 18 cancer study, and we asked cases about their use 19 of cell phones, and we asked controls about their 20 use of cell phones. And while the interpretation 21 of the results of the study were somewhat 22 controversial, there was no generalized phenomenon 23 of cases reporting more cell phone use than 24 controls in that particular study. 25 So that -- I can't think of another</p>

<p style="text-align: right;">Page 162</p> <p>1 example in my career of sort of one of these  2 generally suspected things. I mean, I've studied  3 a lot of occupational exposures, but those tend to  4 be more obscure, and people don't, you know, have  5 the same visceral reaction maybe to were you  6 exposed to formaldehyde or benzene or this or  7 that.  8 BY MS. BRANSCOME:  9 Q For purposes of your meta-analysis, you  10 looked at the binary question of ever having used  11 talc and never having used talc, correct?  12 A Among other -- not only that, but that  13 in addition to, yeah.  14 Q Yes. For example, you were not -- your  15 data isn't stratified based off of having used it  16 to a certain degree of frequency, correct?  17 A The -- the meta-analysis, no.  18 Q Okay.  19 A I -- I looked at dose-response  20 information within the studies that provided it,  21 but I didn't do any meta-analyses of the -- of the  22 dose-response data.  23 Q Okay. So I -- I asked you sort of the  24 broad question about what has changed in the  25 scientific literature with respect to perineal use</p>	<p style="text-align: right;">Page 164</p> <p>1 A Yeah.  2 Q Are those areas in which you contend  3 there is developments in the scientific literature  4 that is relevant to the question of the connection  5 between perineal use of talc and ovarian cancer?  6 A Yes.  7 Q Okay. So I just wanted to talk to you  8 about which of those categories you are  9 independently offering an expert opinion as  10 opposed to you are deferring to others. Does that  11 make sense?  12 A Yes.  13 Q All right. So you are offering an  14 expert opinion about developments in the  15 epidemiology, correct?  16 A Correct.  17 Q Are you testifying as an expert in  18 developments in the scientific literature with  19 respect to toxicology?  20 A No.  21 Q Are you testifying as an expert with  22 respect to developments in the scientific  23 literature in molecular biology?  24 A No. I -- I'm aware that there have been  25 some publications since 2006 in that domain, but</p>
<p style="text-align: right;">Page 163</p> <p>1 of talc since the 2006 IARC Working Group, but I  2 want to point you now sort of specific to what you  3 say in your report and ask you some more detailed  4 questions about what's changed.  5 So if you could turn to page 67 of  6 Exhibit 10 there.  7 A Yes.  8 Q Sorry, just one moment. My pencil has  9 died on me. Just give me one second. All right.  10 All right. So you have a Section 9 here  11 that says: "Contrast with IARC monograph and  12 other reviews." Do you see that?  13 A I do.  14 Q All right. And you asked the question  15 in your report: "What has changed in the years  16 since the IARC review?" Correct?  17 A Correct.  18 Q All right. And you talk about  19 additional studies and scientific literature  20 addressing a variety of topics, including  21 epidemiology, toxicology, molecular biology and  22 mechanistic studies; is that correct?  23 A Sorry, are -- you're saying that I  24 referred to those domains?  25 Q Yes.</p>	<p style="text-align: right;">Page 165</p> <p>1 I'm not offering an opinion about those.  2 Q Are you offering an opinion with respect  3 to the biological mechanism by which the perineal  4 use of talc may or may not cause ovarian cancer?  5 A Not an opinion. Again, I'm -- I'm  6 acknowledging that there is new evidence, and I  7 mention some of that, yes.  8 Q But as an expert, you're not here to  9 opine on the strengths and weaknesses of that  10 evidence or how it might be weighted against other  11 evidence that's in the field related to biological  12 mechanism; is that fair?  13 MS. PARFITT: Objection. Form.  14 THE WITNESS: That's correct.  15 BY MS. BRANSCOME:  16 Q Okay. Now, you state in your report  17 that: "The various possible biases" -- this is  18 still on page 67 -- "that are on the table remain  19 substantially similar to the ones that were  20 considered by the IARC panel." Correct?  21 A Correct, I said that.  22 Q Okay. What are the various possible  23 biases that you refer to there?  24 A Well, I -- I'd have to go back to the  25 IARC 2006 report to give you a full answer, but I</p>

<p style="text-align: right;">Page 166</p> <p>1 guess the main things that were highlighted at the</p> <p>2 time were measurement error, how to assess</p> <p>3 exposure to talc, and what the impact of</p> <p>4 measurement error might be on the estimates,</p> <p>5 recall bias and the possible impact that that</p> <p>6 might have.</p> <p>7 Q What do you mean by "measurement error"?</p> <p>8 A Measurement error is closely related to</p> <p>9 recall bias, but it's not the same thing.</p> <p>10 Measurement -- recall bias refers to differences</p> <p>11 between cases and controls in the way they</p> <p>12 respond. Measurement error refers to inaccurate</p> <p>13 recall and reporting, irrespective of whether</p> <p>14 there are cases and controls. There can be</p> <p>15 exactly the same degree of error in -- in recall</p> <p>16 between cases and controls.</p> <p>17 So it's not differential. It's not --</p> <p>18 it's not a recall bias between the two groups.</p> <p>19 But if there's error, if some people report high</p> <p>20 use, and in fact they had medium use and all --</p> <p>21 all this sort of thing, that impacts the estimates</p> <p>22 of relative risk -- even though those errors are</p> <p>23 the same in the cases and controls, that impacts</p> <p>24 the estimates of relative risk, and that generally</p> <p>25 impacts it in the direction of attenuating the</p>	<p style="text-align: right;">Page 168</p> <p>1 there is error in diagnose -- I guess you -- what</p> <p>2 you're alluding to -- let me make sure, you're</p> <p>3 alluding to possible misdiagnosis between</p> <p>4 mesothelioma and ovarian cancer. Is that where</p> <p>5 you're going?</p> <p>6 Q That -- that is one possibility, yes.</p> <p>7 A So in the case of a -- in this situation</p> <p>8 of a cohort study, following up a group of women,</p> <p>9 some of them really get mesotheliomas that are not</p> <p>10 linked to talc exposure, but those women are</p> <p>11 classified as ovarian cancers erroneously.</p> <p>12 They -- that error would have the effect of</p> <p>13 reducing the apparent risk compared to the real</p> <p>14 risk of talc and ovarian cancer. In that context,</p> <p>15 it would have that effect.</p> <p>16 In the context of a case-control study,</p> <p>17 where you start with a group of women who have</p> <p>18 been diagnosed with ovarian cancer but in truth</p> <p>19 some of them had peritoneal mesotheliomas, and you</p> <p>20 compare them to controls, the women who -- and</p> <p>21 assuming that talc has no effect on peritoneal</p> <p>22 mesothelioma, which is another assumption to make,</p> <p>23 but -- but assuming that it does on ovarian</p> <p>24 cancer, just for the sake of argument, lumping in</p> <p>25 the mesotheliomas with the ovarian cancer cases</p>
<p style="text-align: right;">Page 167</p> <p>1 relative risk estimates, lowering them from what</p> <p>2 they really are.</p> <p>3 So that's one error -- one type of error</p> <p>4 that is -- that permeates epidemiology and that is</p> <p>5 present, and that we have to be conscious of and</p> <p>6 try to evaluate.</p> <p>7 Q Could there be measurement error related</p> <p>8 to misdiagnoses?</p> <p>9 A Yes.</p> <p>10 Q And if there was misdiagnoses in the</p> <p>11 sense that someone was diagnosed with ovarian</p> <p>12 cancer but in fact had a different form of cancer,</p> <p>13 that could actually result in an artificially</p> <p>14 inflated relative risk, correct?</p> <p>15 MS. PARFITT: Objection. Form.</p> <p>16 THE WITNESS: So that kind of error in</p> <p>17 diagnosis has subtly different meaning in the</p> <p>18 context of a case-control study and a cohort</p> <p>19 study. And if -- if you want, I'll -- I could try</p> <p>20 to answer your question in -- in each context.</p> <p>21 BY MS. BRANSCOME:</p> <p>22 Q Okay.</p> <p>23 A So it has an effect in both contexts,</p> <p>24 but it's a slightly different effect.</p> <p>25 So in the context of a cohort study, if</p>	<p style="text-align: right;">Page 169</p> <p>1 would again create a reduction in the estimate of</p> <p>2 relative risk.</p> <p>3 So in both situations -- I would have to</p> <p>4 work it out on a pad of paper, but I think in both</p> <p>5 cases -- and I did write something about this in</p> <p>6 my report, so if you don't --</p> <p>7 Q Feel free to take a look. Sure.</p> <p>8 A -- mind. Thinking out loud in the</p> <p>9 middle of a deposition is sometimes harder than</p> <p>10 thinking out loud at home. (Peruses document.)</p> <p>11 So I'm looking at page 57,</p> <p>12 Section 7.2.5, at the bottom of the page and then</p> <p>13 going on to the next page, and see if what I said</p> <p>14 then is -- corresponds roughly to what I just</p> <p>15 said.</p> <p>16 I think basically it -- it agrees with</p> <p>17 what I just said. Basically the effect would be</p> <p>18 to attenuate estimates in this situation.</p> <p>19 Q So we discussed -- of the various</p> <p>20 possible biases that might affect the</p> <p>21 epidemiology, we talked about measurement error,</p> <p>22 recall bias, diagnostic error.</p> <p>23 Are there any other potential biases</p> <p>24 that should be considered when evaluating the</p> <p>25 epidemiology on the use of talc peritoneally?</p>

<p style="text-align: right;">Page 170</p> <p>1 A Yes. So I -- I did list a bunch of 2 possible biases in my report. And one of them -- 3 if you don't mind, I'll just go through the titles 4 of the different things that -- starting on 5 page 53. 6 Bias due to nonresponse or 7 nonparticipation. If you carry out a case-control 8 study, and you get -- you identify a group of a 9 hundred women who are cases, and you ask them to 10 participate and only 50 agree to participate, and 11 the ones who agree to participate happen to be the 12 only ones who used talcum powder, and the other 50 13 that you don't know about never used it, that 14 would be a problem. And -- but it also depends 15 what happens among the controls. Among the 16 controls, do you get the same nonresponse bias? 17 So there's a -- that is one possible bias in 18 case-control studies. 19 The second one I listed was recall or 20 reporting bias that we've discussed. 21 The third one is what I call 22 nondifferential or random error, which we 23 discussed. It's error in reporting that is equal 24 in cases and controls, but it has an impact on 25 relative risk estimates.</p>	<p style="text-align: right;">Page 172</p> <p>1 other biases. And this is why I corrected you at 2 the beginning when we were talking about 3 confounding and bias. I mean it's not -- I'm not 4 criticizing you in any way for this. It's -- 5 there is terminological gray zones in 6 epidemiology, so it's not always clear. But -- 7 Q Would it be fair to describe a 8 confounding variable in the context of ovarian 9 cancer as something that as of now is unknown that 10 makes a particular individual more likely to 11 develop ovarian cancer that also, for whatever 12 reason, makes them more likely to use talcum 13 powder? 14 A Yes. That would be a correct 15 interpretation of "confounding." 16 Q And that is something that should be 17 taken into account in evaluating the epidemi- -- 18 epidemiological literature, correct? 19 A That's correct. 20 Q And you would agree that the scientific 21 community at large has not yet understood all of 22 the potential factors that might contribute to a 23 susceptibility to develop ovarian cancer, correct? 24 MS. PARFITT: Objection. Form. 25 THE WITNESS: Sorry, I -- I was hearing</p>
<p style="text-align: right;">Page 171</p> <p>1 The fourth one, which we haven't 2 discussed, has to do -- it's mainly a problem for 3 cohort studies. And if you carry out a cohort 4 study of -- focused on cancer, and you collect 5 information about exposure, and then follow them 6 for two years to find out how many of them got 7 cancer, and whether there is a difference between 8 the people who were exposed and the people who are 9 not exposed, well, that would be pretty hopeless 10 because it takes more than two years for cancers 11 to develop and be diagnosed. So short follow-up 12 periods in cohort studies would be a source of 13 bias in cohort studies. 14 Diagnostic errors, we've just discussed. 15 Initiation of powdering as a result of 16 ovarian cancer, is it possible that some women 17 who -- that there is a statistical association 18 between powdering and ovarian cancer, but it's 19 because the women who get ovarian cancer in the 20 early stages, to relieve symptoms or to deal with 21 discomfort start to use powdering. And so that is 22 a potential bias. 23 Confounding is the next category, and 24 that's -- it's a huge category of potential 25 distortion that is a little bit different from the</p>	<p style="text-align: right;">Page 173</p> <p>1 two things with my two ears. 2 MS. PARFITT: Sorry. 3 THE WITNESS: Can you repeat the last 4 part? 5 BY MS. BRANSCOME: 6 Q Yeah. You would agree that all of the 7 factors that might make someone susceptible to 8 developing ovarian cancer are not currently known. 9 A That's correct. 10 So are -- are you -- are you getting at 11 the potential impact of confounding as -- from 12 unknown factors as something that hasn't been 13 properly evaluated or that is part of this 14 picture? 15 Q I am simply asking you -- 16 A Yes. 17 Q -- questions about your opinions. 18 A Yes, yeah. 19 Q But you agree that the possibility of an 20 unknown confounding variable is something that, as 21 an epidemiologist, you would at least consider 22 when looking at the strength of association 23 established by epidemiological studies, correct? 24 A I would consider it, and I've considered 25 it in the context of this literature, and in my</p>

<p style="text-align: right;">Page 174</p> <p>1 opinion, it's unlikely that any confounding factor 2 or factors would create the pattern of results 3 that we see. 4 And if I could give you one piece of 5 evidence about why I -- you know, that illustrates 6 why I think that. A confounding factor can only 7 bias the result by a certain amount; not as strong 8 as its own relationship to the risk factor. 9 So if there's a risk fact- -- if the 10 relative risk that we see around 1.3 -- ballpark, 11 let's for the sake of argument say 1.3 -- is due 12 to a confounding factor, that confounding factor 13 would have to have an association with ovarian 14 cancer much strong -- stronger than 1.3, but much 15 stronger than 1.3. 16 And I can -- just to illustrate that, I 17 actually have a publication -- I think I gave you 18 a copy of that publication of mine that 19 illustrates my own research on occupational causes 20 of cancer -- 21 THE VIDEOGRAPHER: Sorry. 22 THE WITNESS: Am I again disconnected? 23 Okay. When I get excited... 24 Yes, that's the one. If I could -- 25 MS. PARFITT: Make a copy.</p>	<p style="text-align: right;">Page 176</p> <p>1 illustrate the potential impact of confounding in 2 this issue of ovarian cancer and talc, and what -- 3 to explain why I believe that the excess risks 4 that we observe are unlikely to be explained by 5 confounding. 6 Q Okay. You would agree, though, that if 7 there was a confounding variable that had a 8 relationship with, in this case, ovarian cancer 9 that was stronger than 1.3, it could explain an 10 increase of 1.3 associated with the use of talc if 11 it was similarly connected to the use of talcum 12 powder products -- 13 MS. PARFITT: Objection. Form. 14 BY MS. BRANSCOME: 15 Q -- correct? 16 MS. PARFITT: Objection. Form. 17 THE WITNESS: Well, one of the points 18 that I want to illustrate is that not only would 19 it have to be stronger than 1.3, it would have to 20 be a lot stronger than 1.3. 21 BY MS. BRANSCOME: 22 Q How strong would it need to be? 23 MS. PARFITT: Objection. Form. 24 THE WITNESS: I'll answer that by -- by 25 showing you what -- what we found when we were</p>
<p style="text-align: right;">Page 175</p> <p>1 THE WITNESS: Do you have any copies? 2 MS. PARFITT: I'm looking to see. 3 THE WITNESS: So -- well, if I could 4 just read a couple of sentences from the abstract 5 of this, I'll tell you what this is about. It's 6 a study of -- 7 BY MS. BRANSCOME: 8 Q Could you, please, Dr. Siemiatycki, 9 identify for me -- 10 A Oh. 11 Q -- what is the paper from which you are 12 reading. 13 A Yes. This is a paper called "Degree of 14 confounding bias related to smoking, ethnic group, 15 and socioeconomic status in estimates of the 16 associations between occupation and cancer." 17 Q Is this something that you cite to or 18 reference anywhere in the report that you 19 submitted in the MDL? 20 A It's only in my CV, which is I think 21 part of the record. 22 Q What led you to specially identifying 23 this article, which you seem to have handy today 24 here at the deposition? 25 A Because I was thinking about how to</p>	<p style="text-align: right;">Page 177</p> <p>1 examining the associations between different 2 occupations and lung cancer. 3 So occupation and lung cancer, there are 4 some true associations there, as you probably 5 know, but -- and we collected information about 6 people's occupations. We also collected 7 information about their smoking history, their 8 socioeconomic status, their ethnicity and so on. 9 A lot of factors. 10 But the most important part of this was 11 looking at the association between lung cancer and 12 smoking and -- lung cancer and occupation. We 13 chose I think 15 occupations, estimated the odds 14 ratios for 15 different associations between 15 occupations and lung cancer, and we controlled for 16 smoking or we didn't control for smoking. We 17 compared the results when you control for smoking 18 and when you don't compare -- control for smoking. 19 BY MS. BRANSCOME: 20 Q Respectfully, Dr. Siemiatycki, I only 21 have seven hours to ask you questions. 22 A Okay. 23 Q Your -- your -- counsel for the 24 plaintiffs can ask you to fully explain other 25 research that you've done.</p>

<p style="text-align: right;">Page 178</p> <p>1 A Okay.</p> <p>2 Q It sounds very interesting.</p> <p>3 A Thank you.</p> <p>4 Q But my question to you is, in your</p> <p>5 opinion, how strong would an association have to</p> <p>6 be with a confounding variable in order to play a</p> <p>7 significant role in a 1.3 relative risk?</p> <p>8 A My --</p> <p>9 MS. PARFITT: Objection. Form.</p> <p>10 THE WITNESS: -- guess, it would have to</p> <p>11 be in the order of 3 to 5. Because it also</p> <p>12 depends on the association between a talc</p> <p>13 powdering behavior and this unknown confounder.</p> <p>14 BY MS. BRANSCOME:</p> <p>15 Q Okay. Are there limitations to</p> <p>16 performing a meta-analysis?</p> <p>17 MR. TISI: Do you want to mark that or</p> <p>18 no?</p> <p>19 MS. BRANSCOME: No.</p> <p>20 THE WITNESS: Are there --</p> <p>21 BY MS. BRANSCOME:</p> <p>22 Q -- limitations to performing a</p> <p>23 meta-analysis?</p> <p>24 A I -- I'm not sure what -- like --</p> <p>25 Q I believe you referenced earlier that</p>	<p style="text-align: right;">Page 180</p> <p>1 In -- one of the differences between --</p> <p>2 as I mentioned earlier, between -- some types of</p> <p>3 meta-analyses are carried out on clinical trials,</p> <p>4 in fact, I would say the bulk of meta-analysis is</p> <p>5 conducted in clinical trials research where the</p> <p>6 research protocols are really very standardized</p> <p>7 from one study to another, and that enhances the</p> <p>8 ability to make inferences from the results of a</p> <p>9 meta-analysis.</p> <p>10 In observational epidemiology, this</p> <p>11 isn't true. We have very different kinds of study</p> <p>12 design and problems that arise in different</p> <p>13 studies, and this leads in itself to variability</p> <p>14 and heterogeneity. And it is sometimes imagined</p> <p>15 that heterogeneity is a reflection -- some sort of</p> <p>16 a reflection of different risks in different</p> <p>17 populations or something like that. It's mainly</p> <p>18 -- it's at least in part a reflection of the fact</p> <p>19 that different study designs and different -- just</p> <p>20 not just the overall architecture of the design,</p> <p>21 but the implementation, how people were</p> <p>22 interviewed, what the questions were and so on,</p> <p>23 influences the results of a study. That varies</p> <p>24 from study to study, and that creates</p> <p>25 heterogeneity. So --</p>
<p style="text-align: right;">Page 179</p> <p>1 you teach a class on epidemiological</p> <p>2 methodologies; is that correct?</p> <p>3 A Yes.</p> <p>4 Q Okay. So presumably, when you teach a</p> <p>5 class you discuss the strengths and the</p> <p>6 limitations of different types of analyses. Fair?</p> <p>7 A It comes into the course, yes.</p> <p>8 Q Okay. So in the context of looking at</p> <p>9 the strengths and the weaknesses of different</p> <p>10 types of analyses, are there any weaknesses or</p> <p>11 limitations to a meta-analysis?</p> <p>12 A Weakness, okay. Because the word</p> <p>13 "limitation" doesn't always mean weaknesses.</p> <p>14 Meta-analysis depends on having reliable</p> <p>15 data. So the basic studies that you use and the</p> <p>16 basic data that you use in a meta-analysis has to</p> <p>17 be sufficiently reliable to support a good</p> <p>18 meta-analysis.</p> <p>19 The data have to be sufficiently</p> <p>20 comparable in nature. So putting apples and</p> <p>21 oranges and grapes into the same meta-analysis</p> <p>22 would be a problem. Different kinds of apples,</p> <p>23 yes, but different -- et cetera. So you have to</p> <p>24 be careful that you're really measuring the same</p> <p>25 thing, have the same outcomes.</p>	<p style="text-align: right;">Page 181</p> <p>1 Q Does heterogeneity -- do you want</p> <p>2 heterogeneity in a meta-analysis? Is it a good</p> <p>3 thing or does it weaken the meta-analysis?</p> <p>4 A It depends on the purpose of the</p> <p>5 meta-analysis. So some meta-analyses have as one</p> <p>6 of their objectives to identify populations in</p> <p>7 which the effect of the drug or the -- whatever</p> <p>8 you're studying is different from one population</p> <p>9 to another. That is a situation where you want to</p> <p>10 identify heterogeneity, and you want to try to</p> <p>11 target heterogeneity and the different</p> <p>12 populations, different studies, the different</p> <p>13 methods of administering medication, or whatever</p> <p>14 the differences are between studies.</p> <p>15 In observational epidemiology, it's</p> <p>16 rarely the case that heterogeneity -- that a</p> <p>17 formal evaluation of heterogeneity is -- is useful</p> <p>18 or actionable. Usually the bottom line result</p> <p>19 doesn't change. For example, there are</p> <p>20 meta-analyses of smoking and lung cancer where the</p> <p>21 meta-analysis demonstrates heterogeneity of the</p> <p>22 results. The results are always between a</p> <p>23 relative risk of 5 or 6 and a relative risk of 10</p> <p>24 or 12.</p> <p>25 Now, for the question of -- for the</p>

<p style="text-align: right;">Page 182</p> <p>1 qualitative question does smoking cause lung  2 cancer, it really doesn't matter if the relative  3 risk is 5 or 12. So that heterogeneity has  4 absolutely no bearing on the question that is  5 being asked, and the best answer ignore -- would  6 ignore heterogeneity. It doesn't really matter.  7 If you're trying to find out in which  8 populations does smoking have a greater impact,  9 then you might want to say, Okay, let's -- which  10 are the populations where the relative risks were  11 5 and which are populations where the relative  12 risks are 12? Can we identify differences between  13 it? Are they different countries, different  14 ethnic groups, and so on and so forth.  15 So it's a longwinded answer, and I'm not  16 sure if that gets to the question that you were  17 asking.  18 Q Well, you said in your report -- and  19 it's on page 17, if you want to look at it -- you  20 stated -- it's at the top of the page.  21 A Yes.  22 Q "Unless a significant methodological  23 flaw can be identified that has caused the  24 heterogeneity, the best overall estimate remains  25 the meta-estimate."</p>	<p style="text-align: right;">Page 184</p> <p>1 of the weaknesses is that it is sometimes  2 fetishized, and that people put too much -- you  3 know, have sort of a magical belief in the value  4 of meta-analysis result, which is not justified.  5 Often the results of certain critical studies are  6 as valuable or more valuable than those of a  7 meta-analysis, especially when -- especially in  8 observational epidemiology when it's hard to  9 really identify all of the parameters that  10 influence the quality of a study.  11 And so determining what studies to  12 include and which data from each study to include  13 is tricky. It requires judgment. Those judgments  14 can be wrong. They can be contested. Sometimes  15 one very good study is as powerful, but -- it's  16 part of -- a meta-analysis is part of a package of  17 information that I would look at in evaluating the  18 risks.  19 Q Okay. You mentioned the concept that a  20 scientific judgment needs to be used in  21 determining what studies and, more specifically,  22 what data within those studies to include in a  23 meta-analysis, correct?  24 A That's correct.  25 Q And you would agree that -- and I</p>
<p style="text-align: right;">Page 183</p> <p>1 Did I read that correctly?  2 A Yeah. I guess we should read the  3 beginning of the sentence just to -- oh, yes. Oh,  4 yes, I see. Sorry. Yes, I agree with you.  5 Q So what is the basis for that statement?  6 A The basis is that it's correct. Are you  7 offering an alternative to this that I should  8 consider?  9 Q Is there -- I guess my question is, is  10 it -- is it correct because you think it is  11 correct? Or can you point me to something that  12 would support that principle and explain it more  13 fully?  14 A I -- I haven't looked for any  15 documentary evidence that this has been written up  16 in this way anywhere. I've been interpreting  17 meta-analyses in this way, and I believe this to  18 be true.  19 Q Okay. So we talked about a few  20 different things that you articulated as potential  21 weaknesses to a meta-analysis. Are there any  22 other weaknesses to a meta-analysis?  23 A Possibly. Are there any that you can  24 identify? I will be happy to -- you know, I'm  25 just -- to meta-analysis as a concept, I think one</p>	<p style="text-align: right;">Page 185</p> <p>1 believe you just referenced it -- that there can  2 be errors in judgment in determining what studies  3 to include or not include or what data to include  4 or not include, correct?  5 A I --  6 MS. PARFITT: Objection. Form.  7 THE WITNESS: I would not characterize  8 these things as errors in judgment. There can be  9 differences in judgment that are legitimate  10 that -- where people, equally well motivated and  11 well trained and experienced, can arrive at  12 different judgments on some of these things.  13 BY MS. BRANSCOME:  14 Q Did you have a specific methodology that  15 you used in determining which relative risk or  16 odds ratio to include from each of the studies  17 that you include in your meta-analysis?  18 A Carefully reading the study, carefully  19 reading the tables and the reports of what is in  20 the paper, understanding what is there, and then  21 making a determination on that basis.  22 Q And those were, to use your words,  23 quote, judgment calls; is that fair?  24 A Yes.  25 Q Okay.</p>

<p style="text-align: right;">Page 186</p> <p>1 A There is no alternative to judgment in 2 science.</p> <p>3 Q The meta-analysis in your MDL report is 4 different than the meta-analysis in your 2016 5 report; is that correct?</p> <p>6 A The bottom line result, you're saying? 7 Well, yes, but also in the 2016 report, I 8 presented I think eight different estimates, 9 depending on scenarios of which studies to include 10 and which result from which studies to include, 11 because there were some borderline judgments where 12 I thought the best thing would be just -- just 13 provide all of the different options.</p> <p>14 In 2018, I adopted a different strategy. 15 I thought, well, the best service I can provide 16 the court is to give my best estimate of which 17 studies and which data to include, and then to 18 provide a set of alternatives that I call 19 sensitivity analyses. So that's one difference 20 between the two reports.</p> <p>21 Q Okay.</p> <p>22 A But there were some differences in which 23 studies were included and which result in which 24 studies were included from the one to the other.</p> <p>25 Q Well, let me start at the very basic</p>	<p style="text-align: right;">Page 188</p> <p>1 is the difference doing it this way or doing it 2 that way.</p> <p>3 Q Okay.</p> <p>4 A But it's largely overlapped. I mean, 5 I'll look at it and see if I can quickly recognize 6 which studies might have been --</p> <p>7 Q Well, I can point you --</p> <p>8 A Okay. If you've done it, that's great.</p> <p>9 Q Yeah. So you included Green 1997 in 10 your 2016 meta-analysis, correct?</p> <p>11 A Yes.</p> <p>12 Q And you did not include Green 1997 in 13 your 2018 meta-analysis, correct?</p> <p>14 A Correct.</p> <p>15 Q Why did you -- did including Green 1997 16 in your earlier report, do you consider that to be 17 a flaw?</p> <p>18 MS. PARFITT: Objection to form.</p> <p>19 THE WITNESS: I don't consider any of 20 these things flaws. They were judgment calls, and 21 I -- actually, in that case, I learned in between 22 some information that I didn't know in 2016 that 23 made that decision the right one.</p> <p>24 BY MS. BRANSCOME:</p> <p>25 Q What information did you learn?</p>
<p style="text-align: right;">Page 187</p> <p>1 level. Are there any studies that are included in 2 your 2018 meta-analysis that were not available at 3 the time that you did your 2016 meta-analysis?</p> <p>4 A I don't think so.</p> <p>5 Q Okay. So you mention that you made some 6 changes to which studies you included and even 7 within that, some of your numbers are slightly 8 different.</p> <p>9 Can you explain to me what changes you 10 made with respect to which studies to include?</p> <p>11 A So somewhere I did the side-by-side 12 comparison, and I don't think I have -- I don't 13 think I have that with me. So it would take me a 14 bit of time to just compare the two and see how -- 15 how they compare.</p> <p>16 Q So you generated actually a side-by-side 17 comparison of your 2016 meta-analysis and your 18 2018 meta-analysis?</p> <p>19 A Well, of -- of the studies that went 20 into them. Well, generated is a kind of a 21 highfalutin word. I listed on a piece of paper, 22 and then I -- beside it I listed the other ones. 23 So I'm pretty sure I did that at some point just 24 to make sure. If I didn't do it on paper, I did 25 it in my mind. I wanted to know, you know, what</p>	<p style="text-align: right;">Page 189</p> <p>1 A Well, a case-control study was carried 2 out in Australia by a team that involved Green and 3 Purdie, and the publication in 1995, I think it 4 was, described their analysis -- sorry, do you 5 want me to stop while you're --</p> <p>6 Q Keep going.</p> <p>7 A The paper in Purdie 1995, I think it is, 8 described the association between talc and ovarian 9 cancer. I had that in my database.</p> <p>10 And I also had -- a couple of years 11 later, there was a paper by Green that was not 12 focused on talc. It was focused on risks that 13 were related to -- to other -- well, to other 14 gynecological issues in relation to ovarian 15 cancer. But in there she -- in the text, not in 16 any table but in the text, she provided a result 17 on talc and ovarian cancer.</p> <p>18 Because that paper was published in 19 2000 -- in 1997, the Green, et al., paper, I 20 assumed that that was an extension of the 2000 -- 21 of the data that was used for the 1995 paper, and 22 that it actually included more information and 23 more up-to-date information than the 1995 paper 24 published two years earlier. I had some doubts 25 about that. But that was the decision I made in</p>

<p style="text-align: right;">Page 190</p> <p>1 2016. In general, when there were different  2 reports from the same study at different  3 intervals, I took the most recent one as being the  4 more definitive one.  5 When I started analyzing for the 2018  6 report, I had lingering -- I remained with the  7 lingering doubts about the Green study -- the  8 Green report and whether it actually was an  9 updated version of the talc results from 2016 --  10 from my 2016 report.  11 And I wrote to Adele Green, who I know  12 as an acquaintance, not well but enough to write  13 and say, You know, what's going on with these --  14 what was going on with these two papers? Is it  15 the fact that the result -- which one has the most  16 definitive result on talc and ovarian cancer, the  17 earlier one or the more recent one? And she wrote  18 back and said, The earlier one does. That the  19 later one -- and I can't remember the exact  20 explanation, but it had to do with some cases  21 being dropped because of reasons having nothing to  22 do with talc but having to do with other  23 hypotheses that she was examining.  24 So in any case, the two results are  25 identical. So it makes no difference. But that</p>	<p style="text-align: right;">Page 192</p> <p>1 studies over time, the relative risk for the  2 association between peritoneal use of -- I mean  3 perineal use of talc and the development of  4 ovarian cancer has actually gone down?  5 MS. PARFITT: Objection. Form.  6 THE WITNESS: I -- I haven't evaluated  7 that, and I have no reason to agree or disagree  8 with it. If you want me to spend a bit of time  9 looking to see if I can --  10 BY MS. BRANSCOME:  11 Q Well, for example --  12 A -- confirm or --  13 Q You are familiar with the Berge 2018  14 paper, correct?  15 A Yeah, yeah.  16 Q And the authors in that paper said: "We  17 confirm the trend toward lower overall risk  18 estimates as more evidence accumulated."  19 MS. PARFITT: Can we get that article in  20 front of him?  21 MS. BRANSCOME: Of course.  22 MS. PARFITT: Thank you.  23 MS. BRANSCOME: It is tab 48.  24 (A discussion was held off the record.)  25 MS. PARFITT: It's tab 18?</p>
<p style="text-align: right;">Page 191</p> <p>1 is, in answer to your question, why did it change,  2 it wasn't capricious issues. It wasn't wrong. It  3 was the right thing to do.  4 Q Did you retain copies of the e-mail  5 correspondence that you had with Green?  6 A I imagine that I did, but I -- this  7 would have been eight months ago maybe or  8 something.  9 Q Would it be fair to say that you relied  10 on Green's representation of which dataset was  11 more fulsome in determining what to use in your  12 2018 metadata?  13 A Yes.  14 Q And that was something she communicated  15 to you by e-mail, correct?  16 A That's right.  17 MS. BRANSCOME: We can meet and confer  18 about this offline, but we would request  19 production of those e-mails.  20 MS. PARFITT: We'll take it under  21 advisement. Thank you.  22 MS. BRANSCOME: Okay.  23 BY MS. BRANSCOME:  24 Q Do you agree that in terms of the trend  25 for relative risk, with the addition of newer</p>	<p style="text-align: right;">Page 193</p> <p>1 THE WITNESS: Tab 48?  2 BY MS. BRANSCOME:  3 Q Tab 48.  4 A I don't have a tab 48.  5 Q It may be in your second binder.  6 A Oh.  7 MS. PARFITT: I will take this one out.  8 And I'll take this one for you.  9 THE WITNESS: Thank you.  10 MS. PARFITT: Of course.  11 THE WITNESS: Thank you.  12 BY MS. BRANSCOME:  13 Q Dr. Siemiatycki, are you familiar with  14 the article that is located there behind tab 48?  15 A Yes, I am.  16 Q Berge is the lead author on this  17 publication titled "Genital use of talc and risk  18 of ovarian cancer: A meta-analysis." Correct?  19 A Yes, correct.  20 Q I believe earlier you said that Berge  21 "beat you to the punch" might have been the phrase  22 that you used.  23 What did you mean by that?  24 A If this had never appeared, I might have  25 worked on a manuscript to submit for publication</p>

<p style="text-align: right;">Page 194</p> <p>1 on my meta-analysis before today, sometime in the 2 past. 3 Q Do you rely on Berge 2018? 4 MS. BRANSCOME: Let's go ahead and mark 5 that actually as Exhibit 12. 6 (Exhibit No. 12 was marked for 7 identification.) 8 MR. TISI: How long have we been going? 9 How long have we been going? 10 MS. BRANSCOME: Just under five hours. 11 MR. TISI: No, how long have we been 12 going on this one? 13 MS. BRANSCOME: We can take a break 14 if -- do you need a break? 15 MR. TISI: I'm just asking. 16 MS. PARFITT: Do you want a break? 17 THE WITNESS: No, let's finish -- let's 18 finish with this. 19 MS. PARFITT: Okay. 20 (A discussion was held off the record.) 21 BY MS. BRANSCOME: 22 Q Do you rely in forming your opinions on 23 this case on the Berge article that we just marked 24 as Exhibit 12? 25 A I formed my opinions before knowing</p>	<p style="text-align: right;">Page 196</p> <p>1 here that I'm -- I haven't fully integrated into 2 my evaluation of this paper. But I know what's in 3 it. I know what's the other one. I know what's 4 in this one. 5 Q Okay. So back to my question, 6 Dr. Siemiatycki. 7 A Yeah. 8 Q You stated that you believe that the 9 Berge 2018 study supports the conclusions that you 10 have reached in this litigation, and my question 11 to you was, what do you mean by that? 12 A Well, it supports it in a few ways. 13 One -- and from my point of view, the most 14 important one, but probably not for anyone else -- 15 is that they carried out a search of the 16 literature using a much more intensive and -- a 17 much more intensive procedure than I had. I had 18 full confidence in the procedure that I had used, 19 but it was not as long, as lengthy, as costly, et 20 cetera, et cetera, as what -- and the bottom line 21 was that they didn't find any papers -- relevant 22 papers that I hadn't found. So I was very 23 reassured by this. 24 The second thing is that the bottom line 25 meta-analysis result -- well, no, the second thing</p>
<p style="text-align: right;">Page 195</p> <p>1 about this article. 2 Q Do you believe that the Berge 2018 study 3 supports the conclusions that you have reached in 4 your own meta-analysis? 5 A Yes, I think it does. 6 Q In what way? 7 A Well, let me preface that also by saying 8 that there's been a bit of a -- a history to this 9 article of -- I thought the publication -- there 10 was a version published in 2017, which I thought 11 was the definitive version that I've always kept 12 in my binders as the Berge article, and it's only 13 very recently that I actually came upon this 14 particular version, which is not greatly changed 15 from the 2017 but slightly changed, and I haven't 16 fully digested the small changes that have been 17 made. 18 Q If you could -- sorry for the multiple 19 binders, but if you want to look at your first 20 binder, tab 13, we can see if that's the paper 21 that you previously had reviewed as the Berge 22 paper. 23 A I -- I don't mind answering questions in 24 relation to this version. Just -- I just wanted 25 to point out that there are a couple of things</p>	<p style="text-align: right;">Page 197</p> <p>1 is that the actual results that they chose from 2 the different studies were very similar in most 3 cases to the ones I had chosen from the different 4 study. So there was a degree of corroboration 5 there that I was happy about. 6 They adopted a different strategy in one 7 important respect, and that concerned how to deal 8 with the Terry paper and the various components of 9 the Terry paper. And with all due respect to this 10 team, I don't think that there -- theirs was in 11 error. I prefer my approach that maintained the 12 integrity of the pooled analysis, which has some 13 advantages. But there's -- you know, I wouldn't 14 expect any large differences on the bottom line 15 estimates from their strategy or my strategy. And 16 the bottom line results were very similar. 17 They -- also in the previous version, 18 their evaluation of dose-response was, in my view, 19 deficient in not devoting adequate weight to what 20 I think is the most important evidence around 21 dose-response in this area, which is the Terry 22 pooled analysis. They focused on studies which 23 provided results by duration of exposure and by 24 frequency of exposure. And I think it's the 25 combination of those two which is the most</p>

<p style="text-align: right;">Page 198</p> <p>1 important metric.</p> <p>2 And the fact that the Terry analysis was</p> <p>3 able to combine an enormous dataset for evaluating</p> <p>4 dose-response, much greater than any of the</p> <p>5 studies looking at duration or any of the studies</p> <p>6 looking at frequency, meant that in my view they</p> <p>7 missed an opportunity to properly evaluate</p> <p>8 dose-response by cumulative exposure.</p> <p>9 I note very recently that they have --</p> <p>10 they've now used a different statistical procedure</p> <p>11 for evaluating dose-response by duration and</p> <p>12 frequency, which is embodied in their Table 3,</p> <p>13 which I don't fully understand. It seemed -- this</p> <p>14 was the new part of this study, which I haven't --</p> <p>15 I looked quickly in the method section to see a</p> <p>16 description of exactly what they did, and I</p> <p>17 couldn't find it, but I don't deny that it's</p> <p>18 somewhere in the article. I just haven't had time</p> <p>19 to properly evaluate that part of it.</p> <p>20 Q As you sit here today, do you have any</p> <p>21 criticisms of the statistical analysis that they</p> <p>22 performed?</p> <p>23 A All of it? You're referring to all of</p> <p>24 it? Well, I --</p> <p>25 MS. PARFITT: Objection. Form.</p>	<p style="text-align: right;">Page 200</p> <p>1 That's 2016. Okay.</p> <p>2 Q Dr. Siemiatycki, if you could just</p> <p>3 identify for the record where you're looking so I</p> <p>4 can follow along and the record reflects it.</p> <p>5 A Right. I'm looking in my report of 2018</p> <p>6 in the appendix, page 103, Appendix B.</p> <p>7 Q So looking at Appendix B, which also</p> <p>8 helpfully compares Penninkilampi as well, are</p> <p>9 there studies specifically focused on the Berge</p> <p>10 2018 that in your opinion the authors should have</p> <p>11 included in their meta-analysis?</p> <p>12 MS. PARFITT: Objection. Form.</p> <p>13 THE WITNESS: Okay. Well, just</p> <p>14 following this table, I see that Gates 2008 was in</p> <p>15 my report, but not in theirs. Now, it wasn't in</p> <p>16 my main analysis; it was in one of my sensitivity</p> <p>17 analyses. So I have no -- my main analysis and</p> <p>18 their main analysis concurred about Gates.</p> <p>19 The next one that I see that was in my</p> <p>20 analysis but not in theirs was what I call</p> <p>21 Schildkraut B. And Schildkraut B, for the record,</p> <p>22 is -- there's no such study, but I've named it</p> <p>23 Schildkraut B. It's the result of the analysis of</p> <p>24 the Schildkraut study of cases that were</p> <p>25 interviewed before 2014, I think it was.</p>
<p style="text-align: right;">Page 199</p> <p>1 THE WITNESS: I note that their bottom</p> <p>2 line meta-relative risk is lower than the one that</p> <p>3 I estimated. And I'm not sure why that is. To me</p> <p>4 the -- the difference in -- the minor differences</p> <p>5 in the studies included or excluded is not</p> <p>6 sufficient to explain that, and I wonder if it's a</p> <p>7 software issue, of them having used a different</p> <p>8 software for meta-analysis than I used. But it's</p> <p>9 not a criticism necessarily. I just note this</p> <p>10 discrepancy.</p> <p>11 BY MS. BRANSCOME:</p> <p>12 Q Are there any studies that you included</p> <p>13 in your meta-analysis in 2018 that the Berge</p> <p>14 authors failed to consider that you think they</p> <p>15 should have included?</p> <p>16 A So I'll go back to my report, because I</p> <p>17 do have a table outlining that in my report.</p> <p>18 MS. PARFITT: You want your report?</p> <p>19 THE WITNESS: Yeah, my report, back to</p> <p>20 my report.</p> <p>21 MS. PARFITT: Let me get you that.</p> <p>22 BY MS. BRANSCOME:</p> <p>23 Q And we'll take a break after we finish</p> <p>24 this paper.</p> <p>25 A Thank you.</p>	<p style="text-align: right;">Page 201</p> <p>1 BY MS. BRANSCOME:</p> <p>2 Q And we will discuss that in more detail,</p> <p>3 but do you consider it an error for the Berge</p> <p>4 authors to just have taken the Schildkraut 2016</p> <p>5 data as a whole?</p> <p>6 A No, I don't consider it an error. In</p> <p>7 fact, I used it -- not in my main analysis but in</p> <p>8 one of my sensitivity analyses.</p> <p>9 The same with Shushan. So Shushan '96</p> <p>10 was in my -- one of my sensitivity analyses, not</p> <p>11 in my main analysis, and they did not include it</p> <p>12 in their main analysis. So we agreed on the main</p> <p>13 analyses there.</p> <p>14 Terry, I included in mine, and they</p> <p>15 didn't include Terry. They included the component</p> <p>16 parts of Terry.</p> <p>17 So there was no -- there was no study</p> <p>18 that was in my main analysis that was not in</p> <p>19 theirs.</p> <p>20 Q Okay. And looking quickly back at the</p> <p>21 Berge article, coming full circle to the question</p> <p>22 that I started with, if you could look on page 253</p> <p>23 of that paper.</p> <p>24 MS. PARFITT: Yes, 253.</p> <p>25 BY MS. BRANSCOME:</p>

<p style="text-align: right;">Page 202</p> <p>1 Q Under the Discussion section, do you see 2 where I am? 3 A Yes, I do. 4 Q All right. The second paragraph under 5 Discussion from the Berge paper states: "This 6 meta-analysis suggests that genital powder use is 7 associated with a small increased risk of 8 developing ovarian cancer. However, this positive 9 association appears to be limited to the serous 10 histological type and to case-control studies." 11 Did I read that correctly? 12 A You read it correctly. 13 Q It continues on: "This estimate is 14 somewhat lower than that of previous 15 meta-analysis," and in parentheses, it refers 16 specifically to Huncharek and Langseth, colon, "In 17 our cumulative meta-analysis, we confirmed the 18 trend toward lower overall risk estimates as more 19 evidence accumulated." 20 First, did I read that correctly? 21 A You read it correctly. 22 Q Do you have any basis to disagree with 23 the statement by the Berge authors in this 24 paragraph in the Discussion section? 25 MS. PARFITT: Objection. Form.</p>	<p style="text-align: right;">Page 204</p> <p>1 BY MS. BRANSCOME: 2 Q Based on the evidence that's available 3 today, do you think there is strong enough 4 epidemiological evidence to reach a conclusion 5 about the association between talc -- genital talc 6 use and other specific subtypes of ovarian cancer? 7 A I think it becomes very fragile to draw 8 inferences about other types. And in the absence 9 of reliable evidence about other types, you know, 10 especially those that have a smaller fraction of 11 all ovarian cancers than serous type, I think the 12 prudent thing to do is to consider that all 13 ovarian cancers are affected the same way. 14 The same way as with -- we do with lung 15 cancer and smoking and histologic types of lung 16 cancer. While there is some variability in the 17 degree of relative risk between smoking and 18 adenocarcinoma or squamous cell carcinoma or other 19 types, small cell, large cell, for lung cancer, 20 there is some variability in the degree of 21 relative risk. Generally speaking, we say smoking 22 causes cancer. Smoking causes all kinds of -- 23 causes lung cancer, all kinds of lung cancer. 24 Q Are you qualified to evaluate the 25 reasonableness of making an extrapolation from one</p>
<p style="text-align: right;">Page 203</p> <p>1 THE WITNESS: So there are a few 2 statements in this paragraph, not just one. 3 Do you want me to take them one by one? 4 BY MS. BRANSCOME: 5 Q Sure. 6 A So whether "the positive association 7 appears to be limited to the serous histological 8 type," I have some problem with that. I -- I was 9 looking in their publication for which studies -- 10 let me just see if I can -- which studies provided 11 evidence on serous type, and I couldn't find that. 12 In my -- in my analysis, the evidence 13 that I was able to -- to compile that's in this 14 addendum and meta-analyze showed an approximately 15 similar meta-relative risk between serous and all 16 ovarian cancers. 17 So there is no -- I found no evidence 18 that this -- that there was a particular peak of 19 risk for serous types compared to other types. 20 Q As you sit here today -- 21 MS. PARFITT: Are you done -- are you 22 done with your -- is that -- 23 THE WITNESS: Yeah, for -- for that 24 point on serous, yes. 25 MS. PARFITT: Thank you.</p>	<p style="text-align: right;">Page 205</p> <p>1 subtype of ovarian cancer to all types of ovarian 2 cancer in terms of what is biologically plausible? 3 MS. PARFITT: Objection to form. 4 THE WITNESS: My inferences would be 5 based on the statistical and epidemiological 6 evidence, and if there is biological, 7 physiological evidence that would indicate that 8 talcum powder is more likely to influence one type 9 of ovarian cancer than another, I would be 10 absolutely open to that interpretation. 11 BY MS. BRANSCOME: 12 Q All right. So moving along in that 13 paragraph, are there -- 14 A Okay. 15 Q -- any other sentences or portions of 16 sentences with which you disagree? 17 A So, the statement about case-control 18 studies and whether the positive association is 19 limited to case-control studies is -- is a bit 20 contentious. And I understand very well that the 21 evidence does not -- if we only had the cohort 22 studies, if that's all the evidence that existed, 23 it would be fair to say that that evidence does 24 not argue for an association with -- between 25 ovarian cancer and -- so I would -- I'm not -- I</p>

<p style="text-align: right;">Page 206</p> <p>1 guess if I were writing this, I would qualify it                  2 somehow, and -- no, I think I'll just leave --                  3 leave that there, and you may have follow-up                  4 questions about the case-control/cohort                  5 comparison.                  6 Q Is there anything else in this paragraph                  7 in the Discussion section of Berge 2018 with which                  8 you disagree?                  9 MS. PARFITT: And can you refer him to                  10 the left-hand side of the discussion or the                  11 entire --                  12 MS. BRANSCOME: The second full                  13 paragraph in the Discussion section.                  14 MS. PARFITT: Which starts with "An                  15 important."                  16 THE WITNESS: So I -- I think what --                  17 BY MS. BRANSCOME:                  18 Q No, it begins with "This meta-analysis                  19 suggests."                  20 A Yeah. Yeah.                  21 So your question -- the question is                  22 about that sentence that says: "This estimate is                  23 somewhat lower. In our cumulative meta-analysis,                  24 we confirmed the trend towards lower," da, da, da,                  25 and that refers I guess specifically to Figure 4</p>	<p style="text-align: right;">Page 208</p> <p>1 misstates his testimony.                  2 THE WITNESS: It requires looking at                  3 which studies were included in each of these                  4 meta-analyses, and which results were chosen by                  5 the meta-analysis people who did these                  6 meta-analyses from each paper. The meta-analysis                  7 is somewhat sensitive to which studies are                  8 selected and -- so the same study might have been                  9 selected in the 2004 meta-analysis as in the 2016,                  10 but they chose -- they decided to choose an                  11 estimate from -- a result from that paper that                  12 they thought was the most reasonable one and                  13 that's different.                  14 So one would have to do side-by-side                  15 comparisons of which studies were included and                  16 which results before concluding that this is                  17 because of a downward trend. You also need to                  18 know when the data were collected.                  19 You know, I'm not sure if the -- if you                  20 are implying or if they are implying that -- you                  21 know, I -- a declining trend, if there is one, in                  22 meta-analyses -- these are the years of the                  23 meta-analysis, not the years that women were                  24 exposed. So there's no implication -- direct                  25 implication here that the risks to women are</p>
<p style="text-align: right;">Page 207</p> <p>1 on the following page.                  2 Certainly the confidence intervals, if                  3 you look at the confidence intervals of the                  4 meta-estimates in that Figure 4, from 1988 through                  5 2016, everything is embedded in everything. So                  6 from the point of view of statistical variability,                  7 it would be difficult to argue that there is a                  8 real statistical -- statistically meaningful                  9 difference between the trendline from -- through                  10 that whole period.                  11 There is a tendency by eye for a                  12 decline. I don't know in their paper, in the text                  13 whether they've characterized the decline with any                  14 regression coefficients or not. I don't remember.                  15 It seems to me like a rather weak trend to make a                  16 big point about. So I wouldn't disagree with                  17 the -- the point they're making, but I think it's                  18 not strongly supported. There isn't a strong                  19 trend downwards in this line, in this figure.                  20 Q So you would agree with the authors that                  21 there is a downward trend in the risk assessment                  22 over time as more evidence accumulated, but you                  23 might disagree with them about the strength of                  24 that trend. Is that fair?                  25 MS. PARFITT: Objection. Form,</p>	<p style="text-align: right;">Page 209</p> <p>1 declining over time. So if it's only the fact                  2 that meta-analyses carried out at different points                  3 in time showed very slightly different results, I                  4 don't find that a noteworthy observation. But...                  5 BY MS. BRANSCOME:                  6 Q And you agree that meta-analyses are                  7 sensitive to the judgments applied by the authors                  8 of those studies, correct?                  9 A Yes, they are, but to -- to a degree. I                  10 mean you have to weigh the -- the degree of                  11 bias -- or not the bias, but the -- the influence                  12 of particular decisions that you might make.                  13 I've done an analysis looking at what                  14 happens when you include or exclude studies, and                  15 you could exclude any study from my meta-analysis                  16 and you'd find the same result. So if any of                  17 these studies in my meta-analysis are completely                  18 wrong, if they were completely invented, if the                  19 women were never actually interviewed but the                  20 investigator just wrote a paper on a Sunday                  21 afternoon, and you're suspicious that this study                  22 was -- or badly -- whatever, if you take any one                  23 of these studies and take it out of the mix, it                  24 wouldn't affect the meta-relative risk.                  25 MS. BRANSCOME: Okay. I think this is a</p>

<p style="text-align: right;">Page 210</p> <p>1 good place to take a break.</p> <p>2 MS. PARFITT: Very good. Thank you.</p> <p>3 THE VIDEOGRAPHER: We're going off the</p> <p>4 record at 5:07 p.m.</p> <p>5 (Recess.)</p> <p>6 THE VIDEOGRAPHER: This begins disc</p> <p>7 number 5 in the deposition of Jack Siemiatycki.</p> <p>8 We're going back on the record at 5:36 p.m.</p> <p>9 BY MS. BRANSCOME:</p> <p>10 Q One of the decisions that you had to</p> <p>11 make in conducting your meta-analysis was how to</p> <p>12 treat the Schildkraut 2006 study, correct?</p> <p>13 A 2000 --</p> <p>14 Q -- '16.</p> <p>15 A Thank you. Yes.</p> <p>16 Q Okay. For purposes of your</p> <p>17 meta-analysis, you divided Schildkraut 2016 into</p> <p>18 two sets of results, correct?</p> <p>19 A "Divided" isn't quite the right word.</p> <p>20 Q How would you describe it?</p> <p>21 A Because they're not separate, one</p> <p>22 includes the other.</p> <p>23 Q Okay.</p> <p>24 A So just the word "divided" -- I'm not</p> <p>25 sure what the right word is, but there were two</p>	<p style="text-align: right;">Page 212</p> <p>1 Q But if it's your preference to look at</p> <p>2 the paper now, it is tab 15.</p> <p>3 A It's in this binder, I think.</p> <p>4 MS. PARFITT: Here it is. Thank you.</p> <p>5 THE WITNESS: Thank you.</p> <p>6 Okay. The -- so one includes all --</p> <p>7 Schildkraut A includes all of the cases</p> <p>8 interviewed the whole period, and the</p> <p>9 Schildkraut B includes cases after 2014, but I'm</p> <p>10 not sure if it includes 2014. But...</p> <p>11 BY MS. BRANSCOME:</p> <p>12 Q Let me ask a clarification on that one,</p> <p>13 Dr. Siemiatycki.</p> <p>14 Schildkraut 2016-B shows results for</p> <p>15 individuals interviewed before 2014, correct?</p> <p>16 A I'm sorry, which one, B? Schildkraut B?</p> <p>17 Q Schildkraut 2016-B.</p> <p>18 A B.</p> <p>19 Q I believe you just stated after, so I --</p> <p>20 A I see. Okay.</p> <p>21 Q -- wanted to seek clarification there.</p> <p>22 A Okay. Yeah, I'm --</p> <p>23 Q If it's helpful --</p> <p>24 A It's late in the day. Let me --</p> <p>25 Q Sure. If it's helpful to you to</p>
<p style="text-align: right;">Page 211</p> <p>1 sets of results reported, and I used both sets of</p> <p>2 results. One is embedded -- one set is embedded</p> <p>3 in the other.</p> <p>4 Q So correct me if I'm wrong, Schildkraut</p> <p>5 2016-A shows results from all subjects who were</p> <p>6 interviewed in the study from 2010 through 2015.</p> <p>7 Schildkraut 2016-B is a subset of that that</p> <p>8 includes the results for subjects who were</p> <p>9 interviewed before 2014, correct?</p> <p>10 MS. PARFITT: And, Counsel, if we could</p> <p>11 get Schildkraut in front of him, would that be all</p> <p>12 right?</p> <p>13 MS. BRANSCOME: Sure.</p> <p>14 BY MS. BRANSCOME:</p> <p>15 Q If you need to reference it --</p> <p>16 MS. PARFITT: Sure.</p> <p>17 BY MS. BRANSCOME:</p> <p>18 Q -- to answer my questions, certainly.</p> <p>19 A If you're going -- yes, I think you're</p> <p>20 right in what you said, but if you want me to look</p> <p>21 at specific results in the paper, maybe I should</p> <p>22 have it in front of me.</p> <p>23 Q I was going to direct you there when we</p> <p>24 got to those questions.</p> <p>25 A Okay.</p>	<p style="text-align: right;">Page 213</p> <p>1 reference in your report, you discuss your</p> <p>2 separation of Schildkraut on page 74, Note 6.</p> <p>3 A That's why I wanted my report in a small</p> <p>4 binder, rather than -- before 2014, yes.</p> <p>5 Q And the reason that you divided --</p> <p>6 separated the study into those two groups, one</p> <p>7 which is inclusive of the other, is to account for</p> <p>8 the possibility that publicity surrounding two</p> <p>9 class action lawsuits on talc and ovarian cancer</p> <p>10 in 2014 may have induced bias in the validity of</p> <p>11 reporting talc exposure; is that correct?</p> <p>12 A That's correct.</p> <p>13 Q Okay. But in your main meta-analysis</p> <p>14 you use Schildkraut A, which includes all subjects</p> <p>15 interviewed from 2010 to 2015, correct?</p> <p>16 A That's correct.</p> <p>17 Q When you substituted Schildkraut B,</p> <p>18 which included only subjects interviewed before</p> <p>19 2014, for Schildkraut A, all subjects interviewed</p> <p>20 from 2010 to 2015, the relative risk estimate for</p> <p>21 the meta-analysis goes down, correct?</p> <p>22 A Yes. From 1.28 to 1.27.</p> <p>23 MS. BRANSCOME: If we could mark</p> <p>24 Schildkraut as Exhibit 13.</p> <p>25 THE WITNESS: There's a label here</p>

<p style="text-align: right;">Page 214</p> <p>1 already.</p> <p>2 MS. PARFITT: There is. I will go ahead</p> <p>3 and just -- you don't care -- there's a defense</p> <p>4 label of 1436. Can I go ahead and put the exhibit</p> <p>5 over top of it? Does it matter to you? Okay.</p> <p>6 This will be 13.</p> <p>7 (Exhibit No. 13 was marked for</p> <p>8 identification.)</p> <p>9 BY MS. BRANSCOME:</p> <p>10 Q All right. If you could,</p> <p>11 Dr. Siemiatycki, please turn to Table 2, which is</p> <p>12 on page 1414 of Exhibit 13.</p> <p>13 A I see it.</p> <p>14 Q Before doing that, can you just simply</p> <p>15 confirm that Exhibit 13 is in fact the Schildkraut</p> <p>16 study?</p> <p>17 A Yes, it is.</p> <p>18 Q And we see in Table 2 that there is a</p> <p>19 category for interview date less than 2014, and</p> <p>20 then another category for interview date greater</p> <p>21 than 2014. Correct?</p> <p>22 A Yes, I see that.</p> <p>23 Q All right. And we see that there are</p> <p>24 odds ratios for any genital use for both of these</p> <p>25 categories, correct?</p>	<p style="text-align: right;">Page 216</p> <p>1 A Yes, that's correct.</p> <p>2 Q All right. And the -- those are for the</p> <p>3 cases, meaning individuals who had been diagnosed</p> <p>4 or reported as diagnosed with ovarian cancer,</p> <p>5 correct?</p> <p>6 A Correct.</p> <p>7 Q And if you compare that against the</p> <p>8 controls, 34 percent is the reported number for</p> <p>9 women without ovarian cancer who reported any</p> <p>10 genital use of talcum powder that were interviewed</p> <p>11 before 2014, correct?</p> <p>12 A That's correct.</p> <p>13 Q And if we look at those same</p> <p>14 percentages for the individuals who were</p> <p>15 interviewed after 2014, the percentage of cases,</p> <p>16 meaning individuals who have been diagnosed or</p> <p>17 reported as diagnosed with ovarian cancer who</p> <p>18 claim to have used talc genitally at any point in</p> <p>19 time, goes up to 51.5 percent compared to a</p> <p>20 control of 34.4 percent, correct?</p> <p>21 A That's correct.</p> <p>22 Q All right. And so if we compare</p> <p>23 individuals interviewed before 2014 who have been</p> <p>24 diagnosed or reported as diagnosed with ovarian</p> <p>25 cancer to those individuals in the same category</p>
<p style="text-align: right;">Page 215</p> <p>1 A Yes, I see that.</p> <p>2 Q And the odds ratio for any genital use</p> <p>3 for individuals who were interviewed after 2014 is</p> <p>4 higher than the odds ratio for any genital use for</p> <p>5 those individuals who were interviewed before</p> <p>6 2014, correct?</p> <p>7 A That's correct.</p> <p>8 Q And it also shows the number of</p> <p>9 individuals that fell in those respective</p> <p>10 categories, correct?</p> <p>11 A Yes, correct.</p> <p>12 Q And so just simply looking at the</p> <p>13 reported data, the percentage of women with --</p> <p>14 with ovarian cancer who reported any genital use</p> <p>15 of talc who were interviewed before 2014 was</p> <p>16 36.5 percent, correct?</p> <p>17 A Can you run that by me again? Show me</p> <p>18 where the --</p> <p>19 Q Sure.</p> <p>20 A So interview date before 2014, any</p> <p>21 genital use, the percentage 36.5, number 128, is</p> <p>22 that what --</p> <p>23 Q Yes.</p> <p>24 A -- you are looking at? Okay.</p> <p>25 Q Was that correct?</p>	<p style="text-align: right;">Page 217</p> <p>1 who were interviewed after 2014, you see at least</p> <p>2 a 12 percent increase in those figures; is that</p> <p>3 correct?</p> <p>4 A 12 percent representing which -- which</p> <p>5 two numbers?</p> <p>6 Q Representing the difference between the</p> <p>7 cases who reported genital use of talcum powder --</p> <p>8 A The 36.5?</p> <p>9 Q -- as compared to the 51.5 percent.</p> <p>10 A So you -- you said it's 12 percent? I</p> <p>11 think it's like 14 percent.</p> <p>12 Q It is.</p> <p>13 A Okay.</p> <p>14 Q That is correct.</p> <p>15 But if you do the same comparison for</p> <p>16 the control group, you don't see a similar</p> <p>17 increase or a similar difference in the reporting</p> <p>18 percentages for individuals interviewed before</p> <p>19 2014 as after 2014, correct?</p> <p>20 A That's correct.</p> <p>21 Q Okay. Are those results compatible with</p> <p>22 the existence of recall bias for individuals</p> <p>23 interviewed after 2014?</p> <p>24 A I would say they are compatible with</p> <p>25 recall bias.</p>

<p style="text-align: right;">Page 218</p> <p>1 Q Okay. Was litigation-related recall 2 bias considered by IARC as a possible bias that 3 could explain the association between perineal 4 talc use and ovarian cancer? 5 A In 2006? 6 Q Correct. 7 A I -- I can't remember verbatim the 8 discussions, and I can't remember a discussion of 9 litigation-related impact on response bias. I 10 doubt if there would have been any at that time, 11 but -- and I don't recall any discussion of it. 12 Q And at least the Schildkraut authors are 13 identifying 2014 as a significant year with 14 respect to widespread knowledge of lawsuits 15 involving talcum powder and a claim of ovarian 16 cancer -- 17 MS. PARFITT: Objection. Form. 18 BY MS. BRANSCOME: 19 Q -- correct? 20 MS. PARFITT: Objection. Form. 21 THE WITNESS: I -- if you may, I think 22 what they refer to is localized publicity, not 23 widespread publicity. 24 BY MS. BRANSCOME: 25 Q If you can, can you refer me to the</p>	<p style="text-align: right;">Page 220</p> <p>1 column seems to suggest that data was collected 2 from a number -- 3 A Oh. 4 Q -- of different states across the United 5 States, correct? 6 A Correct. Correct. 7 Q And so at least based on your review as 8 you sit here today, the authors do not seem to 9 have limited the potential effect of publicity of 10 the class action lawsuits to a precise region, 11 correct? 12 A That seems to be the case. 13 Q Okay. 14 A Yes. 15 Q And so your understanding or your 16 testimony earlier that the publicity was only 17 localized, you're not able to point me to anything 18 in the article to support that, correct? 19 A That's correct. 20 Q And in fact, in the two portions of the 21 Schildkraut article that discuss the publicity, 22 there is no specific reference to it being limited 23 to an area, correct? 24 MS. PARFITT: Objection. Form. 25 THE WITNESS: In the two -- sorry.</p>
<p style="text-align: right;">Page 219</p> <p>1 language in the paper that references that. 2 A So I see a mention of it in the -- on 3 page 1412, second column, last paragraph, about 4 seven or eight lines from the bottom, the sentence 5 beginning: "Two class action lawsuits were filed 6 in 2014 concerning possible carcinogenic effects 7 of body powder, which may have influenced recall." 8 Now, there's a reference there, but the 9 reference doesn't indicate where those class 10 actions were. And now I'm going to look in the 11 Discussion section to see if there's any 12 indication. If anyone knows whether there is or 13 if there is not -- I haven't looked for this 14 specifically. I just have a vague memory of them 15 referring to localized publicity, but... (peruses 16 document.) 17 Well, in my very quick scanning, I don't 18 see reference to these being local. You people 19 might know whether these two lawsuits that they 20 refer to in the Reference section, whether they 21 were local in this area. And this is North 22 Carolina, is it? 23 Q Well, so that's -- that's a question I 24 have for you, Dr. Siemiatycki. On page 1412, the 25 paragraph -- the last full paragraph on the second</p>	<p style="text-align: right;">Page 221</p> <p>1 BY MS. BRANSCOME: 2 Q So there's one discussion of the 3 potential public -- the potential effect of 4 publicity, which is on page 1412. 5 A Yeah. 6 Q And then there is a second discussion of 7 it on page 1416 -- 8 A Yes. 9 Q -- in the Discussion section, and 10 neither of those two sections talk about awareness 11 of the class action lawsuits being limited to a 12 specific geographic region, correct? 13 A That's correct. 14 Q In fact, the language that the authors 15 use is a heightened awareness of the exposure as a 16 result of two recent class action lawsuits, and 17 they discuss just publicity, correct? 18 A Yes, I think so. 19 Q Okay. Are you relying -- 20 A In that second paragraph in the 21 discussion, the authors seem to discount the -- 22 the recall bias hypothesis or to minimize it, and 23 I -- I -- I don't support -- or the opposite of 24 what they're saying. I just note that they don't 25 seem to be enthusiastic about that hypothesis that</p>

<p style="text-align: right;">Page 222</p> <p>1 it's strictly due to response bias.  2 But go ahead and --  3 Q The authors do recognize, though, that  4 there is a possibility of recall bias may have  5 caused some inflation of the odds ratios, correct?  6 A Yes.  7 MS. PARFITT: Wait, that's part --  8 that's part of the sentence. Objection.  9 THE WITNESS: Yeah. Yeah.  10 BY MS. BRANSCOME:  11 Q Are you relying on Penninkilampi 2018  12 for your opinions in this litigation?  13 A My opinions were informed before I knew  14 about that article.  15 Q Do you believe that the Penninkilampi  16 2018 study supports your conclusions in this  17 litigation?  18 A It's consistent with my conclusions. A  19 little bit like Berge, the fact that they didn't  20 pick up any studies that I hadn't -- that I had  21 not picked up reassures me that there was nothing  22 amiss in my search of the literature.  23 There were some differences in which  24 studies they included in their meta-analysis and  25 which data. I'm happy with the decisions -- the</p>	<p style="text-align: right;">Page 224</p> <p>1 impact on the bottom line result. Some errors  2 might have large effects, so it would depend what  3 the errors were.  4 But since his studies were mostly the  5 same as the ones I had used and the same ones that  6 Berge had used, and since the results that he had  7 taken out of those studies were mostly the same  8 ones I had taken out and that Berge had taken out,  9 I fully expected his bottom line meta-analysis to  10 produce the same results.  11 BY MS. BRANSCOME:  12 Q The Penninkilampi study does not  13 consider or include the Gates 2010 cohort study,  14 correct?  15 A Correct.  16 Q Do you think Gates 2010 - and if you  17 would prefer to refer to Penninkilampi, it is  18 tab 20.  19 A Yeah.  20 Q In your opinion, is --  21 MS. PARFITT: I have a clean one right  22 here with the -- if we use two books, we can do it  23 to save time, but --  24 THE WITNESS: Sorry?  25 MS. PARFITT: Do you want that?</p>
<p style="text-align: right;">Page 223</p> <p>1 judgments I had made about it. So there are some  2 minor variations there. But essentially they  3 found the same thing that I found, because we're  4 all working with the same data.  5 Q Okay. Did you do an independent  6 verification that the data Penninkilampi reports  7 in his article is indeed accurate?  8 MS. PARFITT: Objection. Form.  9 THE WITNESS: By the data, you mean the  10 results that he put into his meta-analysis?  11 BY MS. BRANSCOME:  12 Q For example, did you look at the  13 reported data in the tables in the Penninkilampi  14 article and compare it to the underlying studies  15 to see if they matched?  16 A I don't recall doing that comparison.  17 I'm not sure why I would want to.  18 Q If there were errors in the reporting of  19 any of the odds ratios or confidence intervals in  20 the Penninkilampi 2018 paper, would that call into  21 reliability the meta-analysis, in your opinion?  22 MS. PARFITT: Objection. Form.  23 THE WITNESS: It depends on the nature  24 of the errors. If there was one decimal point  25 typo sort of thing, it would have absolutely no</p>	<p style="text-align: right;">Page 225</p> <p>1 THE WITNESS: No. I'm actually looking  2 for my copy of the Gates 2010.  3 You're going to ask me about his use  4 of -- Gates 2010?  5 BY MS. BRANSCOME:  6 Q I was simply just going to ask you, is  7 Gates 2010 a significant study, in your opinion,  8 to leave out of a meta-analysis on this topic?  9 MS. PARFITT: Objection. Form.  10 THE WITNESS: A significant study.  11 It -- in my view there are flaws with that study,  12 but there are flaws with many epidemiologic  13 studies. It's not -- that's not a reason to  14 exclude them. I would include it but take note of  15 the flaws, including the fact that their reference  16 category for their odds ratios for their relative  17 risk estimates was not an unexposed group, but it  18 was a group that combined women who had never used  19 talc with women who had used it occasionally.  20 BY MS. BRANSCOME:  21 Q Are there any other errors in the Gates  22 2010 study? And if you'd like to refer to it --  23 MS. PARFITT: Thank you.  24 THE WITNESS: Okay. Let me find my copy  25 of -- yeah, here we are -- Gates 2010.</p>

<p style="text-align: right;">Page 226</p> <p>1 Well, yes, there are some flaws with it, 2 but they're related to the fact that this builds 3 on the Nurses' Health Study, which is a good and 4 well deservedly recognized, good prospective 5 cohort study which focused on many factors in 6 women's lives, including predominantly nutritional 7 reproductive, hormonal factors, and all kinds of 8 diseases, all heart disease, diabetes, et cetera, 9 et cetera. There have been hundreds and hundreds 10 of publications that have come out of it. 11 Their collect- -- the collection of talc 12 information in the Nurses' Health Study was very 13 weak. The questionnaire was conducted in 1982. 14 It was part of a biannual follow-up mailed 15 questionnaire. The question itself and the 16 structure of the question itself I find very weak 17 from the point of view of designing questions for 18 questionnaires. I mean, I -- I could read it into 19 the record, but it's in the -- it's in the -- it's 20 quoted in the Gertig paper, and it's actually -- 21 I've seen that page of the questionnaire, and 22 it's -- I find it ambiguous as to how women would 23 answer that question. 24 And it's only one question for that 25 point in time. There was never any follow-up. So</p>	<p style="text-align: right;">Page 228</p> <p>1 authors of the Penninkilampi 2018 publication? 2 A No, I don't. 3 Q Do you know or have any information 4 about the source or sources of funding for the 5 Penninkilampi article? 6 A No, I don't, no. I -- I would add, 7 though, that the inclusion or exclusion of Gates 8 2010 probably didn't affect the bottom line result 9 of their meta-analysis by more than 0.01 decimal 10 point of the odds ratio. 11 Q But did they publish any type of 12 sensitivity analysis that would let you 13 specifically draw that conclusion? 14 A Well, I -- I have done one myself where 15 I dropped each of the studies in order to see what 16 would be the impact if that study had been 17 dropped. And there's hardly -- no study has more 18 than a 1 decimal -- you know, 0.01 decimal point 19 on the odds ratio. 20 So we could argue about the merits of 21 any of these studies or demerits, but the impact 22 of including them or excluding an individual study 23 is pretty minimal. 24 Q Shushan 1996 is one of the studies you 25 did not include in your main meta-analysis,</p>
<p style="text-align: right;">Page 227</p> <p>1 between 1982 and 2007 or so, when the follow-up of 2 the -- for the Gates analysis ended, they had no 3 idea whether women were exposed -- whether women 4 who had been exposed in 1982 were in exactly the 5 same exposure category in 1990, in 2000, in 2005 6 and so on. They made the assumption that women's 7 exposure status was stable for 25 years. And so 8 that's a major weakness of the analysis of talc 9 and ovarian cancer in -- from this study. 10 BY MS. BRANSCOME: 11 Q So in your view, was it proper for the 12 Penninkilampi authors to leave Gates 2010 out of 13 their meta-analysis? 14 A That's not what I said. That's not what 15 I said. 16 I -- I think to go down the road of 17 making value judgments about each of these studies 18 and including them or not including them would end 19 up in the need for many days of deposition and 20 cross-examination, because each of those -- any 21 decision about any study can be argued umpteen 22 ways. And that's why I took the decision early on 23 not to make exclusions based on my judgment of the 24 quality of the study. 25 Q Do you personally know any of the</p>	<p style="text-align: right;">Page 229</p> <p>1 correct? 2 A Correct. 3 Q And you reported that you did not 4 include it because the report was quite cryptic 5 regarding the data collection and the talc 6 exposure variable, correct? 7 A That's correct. 8 Q What did you mean by the report was 9 quite cryptic regarding the data collection? 10 A So I have to take a couple of minutes to 11 review that -- to look at that paper to answer 12 your question. 13 Well, so the first thing that strikes 14 me -- and I haven't read the description of how 15 they collected the data. The first thing that 16 strikes me is they have a table, Table 2 on 17 page 15, with some information about these various 18 variables, including talc exposure. And the two 19 categories of talc exposure that they describe in 20 this table, one is called "Never - seldom," and 21 the other one is called "Moderate - a lot." I 22 don't know what that means. So that's one 23 element -- how they present it and how they 24 analyze the data. 25 But I think actually how they collected</p>

<p style="text-align: right;">Page 230</p> <p>1 the data also led me to describe the -- the 2 information on exposure as being cryptic. 3 Q Okay. Are you familiar with the 2018 4 paper by Mohamed Taher and others entitled "The 5 systematic review and meta-analysis: The 6 association between perineal use of talc and risk 7 of ovarian cancer"?</p> <p>8 A Yes, I am.</p> <p>9 Q Okay. Have you read the Taher 2018 10 manuscript?</p> <p>11 A Yes. I haven't read all the appendices, 12 but I basically read enough that I know what's in 13 it.</p> <p>14 Q Did you have access to the Taher 2018 15 article before it was published?</p> <p>16 A I don't think it's been published.</p> <p>17 Q How did you get access to the Taher 18 manuscript and the appendices?</p> <p>19 A I heard about -- I first heard about the 20 Canadian Department of Health advisory, or 21 whatever the word is, about talc and ovarian 22 cancer in the public media. And I -- I think in 23 the news report that I saw, there was a reference 24 to Taher -- the Taher paper. That's how I first 25 learned about something by them.</p>	<p style="text-align: right;">Page 232</p> <p>1 Q Which author do you know?</p> <p>2 A Daniel Krewski.</p> <p>3 Q You have published many papers with, is 4 it, Dr. Krewski?</p> <p>5 A Yes.</p> <p>6 Q Is that correct?</p> <p>7 A Yes. Yes, it is.</p> <p>8 Q How many papers have you published with 9 him?</p> <p>10 A I'll look at my CV and count.</p> <p>11 Q Would it be fair to say over 20?</p> <p>12 A Oh, I would be surprised if it was that 13 high. But if you've counted, I won't contradict 14 what you -- what you say.</p> <p>15 Q Let's do it this way: Would all of the 16 papers that you have coauthored with Dr. Krewski 17 be listed on your CV?</p> <p>18 A Yes.</p> <p>19 Q Have you discussed your opinion on talc 20 and ovary -- ovarian cancer with Dr. Krewski?</p> <p>21 A No.</p> <p>22 Q Have you discussed your opinion on talc 23 and ovarian cancer with any of the authors of the 24 Taher manuscript?</p> <p>25 A No.</p>
<p style="text-align: right;">Page 231</p> <p>1 And I wrote to Ms. Parfitt -- I sent a 2 message to Ms. Parfitt asking her if she knows 3 anything about this and has that information, and 4 she wrote back, I think, and said, No, I thought 5 you might have -- know something about it and have 6 information.</p> <p>7 MS. PARFITT: And -- and, 8 Dr. Siemiatycki, you're not to discuss --</p> <p>9 THE WITNESS: Okay.</p> <p>10 MS. PARFITT: -- discuss our 11 communications.</p> <p>12 THE WITNESS: Okay.</p> <p>13 Subsequently, Ms. Parfitt sent me the 14 Taher paper.</p> <p>15 BY MS. BRANSCOME:</p> <p>16 Q And when -- when did you first request 17 the Taher paper and appendices from Ms. Parfitt?</p> <p>18 A I think in December 2018.</p> <p>19 Q When were you provided with the Taher 20 manuscript and the appendices and supplemental 21 tables?</p> <p>22 A Within a few days after that.</p> <p>23 Q Do you know personally any of the 24 authors on the Taher manuscript?</p> <p>25 A I know one of them.</p>	<p style="text-align: right;">Page 233</p> <p>1 Q Have you spoken to or otherwise 2 communicated with Dr. Krewski about your 3 involvement as an expert in this litigation?</p> <p>4 A No, I haven't.</p> <p>5 Q Do you know if the Taher manuscript has 6 been accepted for publication?</p> <p>7 A I don't know if it's been submitted for 8 publication.</p> <p>9 Q Do you know anything about the source or 10 sources of funding for the Taher 2018 manuscript?</p> <p>11 A I don't have any privileged information 12 about that, but I seem to recall in the manuscript 13 they're saying something about funding from Health 14 Canada.</p> <p>15 Q Is it fair to say that your knowledge 16 with respect to the source or sources of funding 17 of the Taher manuscript is limited to what is 18 written in the manuscript itself?</p> <p>19 A Yes.</p> <p>20 Q Did you attend the National Cancer 21 Institute directors meeting held in Lyon, France, 22 on July 11th through 13th, 2018?</p> <p>23 A No, I did not.</p> <p>24 Q Now, the Taher 2018 manuscript contains 25 a meta-analysis, correct?</p>

<p style="text-align: right;">Page 234</p> <p>1 A Correct.</p> <p>2 Q And Taher 2018 calculates an overall</p> <p>3 relative risk of 1.28, correct?</p> <p>4 MS. PARFITT: If we could just get that</p> <p>5 in front of him.</p> <p>6 MS. BRANSCOME: Oh, of course.</p> <p>7 MS. PARFITT: Do you have your copy? I</p> <p>8 appreciate that.</p> <p>9 MS. BRANSCOME: It is tab --</p> <p>10 MS. PARFITT: I think he may have it as</p> <p>11 well and --</p> <p>12 THE WITNESS: I have it --</p> <p>13 MS. PARFITT: Make that a little easier</p> <p>14 and more quicker.</p> <p>15 MR. TISI: Do you want to mark it?</p> <p>16 MS. BRANSCOME: We have already marked</p> <p>17 Dr. Siemiatycki's binder.</p> <p>18 MR. TISI: Okay. We can --</p> <p>19 MS. BRANSCOME: I believe that contains</p> <p>20 the -- the manuscript and the exhibits.</p> <p>21 MS. PARFITT: And that is binder 6,</p> <p>22 Exhibit 6.</p> <p>23 MR. TISI: You said binder, going with</p> <p>24 his or the one --</p> <p>25 MS. PARFITT: Exhibit 6.</p>	<p style="text-align: right;">Page 236</p> <p>1 one in the binders you gave him? That may help.</p> <p>2 MS. BRANSCOME: It's tab 31.</p> <p>3 MS. PARFITT: Thank you.</p> <p>4 Tab 31. I appreciate that.</p> <p>5 No, you can keep yours.</p> <p>6 THE WITNESS: Okay.</p> <p>7 MS. PARFITT: There you go, just for the</p> <p>8 record. Okay. Thank you.</p> <p>9 BY MS. BRANSCOME:</p> <p>10 Q So my question to you, Dr. Siemiatycki,</p> <p>11 is Taher 2018 calculates an overall relative risk</p> <p>12 of 1.28. Is that correct?</p> <p>13 A That's what it says in the abstract,</p> <p>14 yes.</p> <p>15 Q And the confidence interval that they</p> <p>16 report is 1.2 to 1.37, correct?</p> <p>17 A Yes.</p> <p>18 Q So the overall relative risk as well as</p> <p>19 the confidence interval reported in the Taher 2018</p> <p>20 paper is very similar to the overall relative risk</p> <p>21 and confidence interval that you report in your</p> <p>22 analysis for the MDL, correct?</p> <p>23 A That's correct. Which is not</p> <p>24 surprising.</p> <p>25 Q And if you could turn to page 49 of the</p>
<p style="text-align: right;">Page 235</p> <p>1 MS. BRANSCOME: Exhibit 6 is</p> <p>2 Dr. Siemiatycki's copy of the Taher manuscript</p> <p>3 with the appendices and supplemental tables.</p> <p>4 BY MS. BRANSCOME:</p> <p>5 Q Is that correct?</p> <p>6 A That's correct.</p> <p>7 MR. TISI: And that's in his binder,</p> <p>8 Exhibit 6.</p> <p>9 THE WITNESS: I don't -- I didn't bring</p> <p>10 the supplemental tables and appendices with me.</p> <p>11 BY MS. BRANSCOME:</p> <p>12 Q Okay. So could you just describe for</p> <p>13 the record the contents of Exhibit 6. It is</p> <p>14 marked, but just so that I can follow along.</p> <p>15 A This document?</p> <p>16 MR. TISI: No, the whole thing.</p> <p>17 THE WITNESS: Oh, the whole -- the whole</p> <p>18 thing. It contains various meta-analyses, so the</p> <p>19 Berge, Penninkilampi, Huncharek, just the meta --</p> <p>20 main meta-analyses that have been done.</p> <p>21 MS. PARFITT: And, Counsel --</p> <p>22 THE WITNESS: Langseth.</p> <p>23 MS. PARFITT: Right.</p> <p>24 -- in light of the fact he has his in</p> <p>25 front of him, Exhibit 6, is there a corresponding</p>	<p style="text-align: right;">Page 237</p> <p>1 Taher paper. You see the Conclusion section?</p> <p>2 A Yes.</p> <p>3 Q The authors of the Taher paper state in</p> <p>4 the Conclusion section: "Consistent with previous</p> <p>5 evaluations, the IARC in 2010 and subsequent</p> <p>6 evaluations by individual investigators, the</p> <p>7 present comprehensive evaluation of all currently</p> <p>8 available relevant data indicates that perineal</p> <p>9 exposure to talc powder is a possible cause of</p> <p>10 ovarian cancer in humans."</p> <p>11 First, did I read that correctly?</p> <p>12 A Yes.</p> <p>13 Q Okay. Do you agree first that the Taher</p> <p>14 2018 paper represents a comprehensive evaluation</p> <p>15 of all currently available relevant data?</p> <p>16 A Yes. I haven't -- I haven't done the</p> <p>17 same comparison between which studies and which</p> <p>18 data points from each study they used compared to</p> <p>19 the ones that I've used. I did that for the Berge</p> <p>20 and for the Penninkilampi, comparing theirs with</p> <p>21 mine. I haven't done that for theirs. So I -- I</p> <p>22 assume that they used basically the same studies</p> <p>23 and the same results from each study.</p> <p>24 But, you know, to answer -- I'm quite</p> <p>25 sure that they did this comprehensive evaluation</p>

<p style="text-align: right;">Page 238</p> <p>1 of all currently available, but to answer that 2 strictly, I would want to do a comparison of the 3 two. But I'm willing to accept. 4 Q Okay. And we see here even in this 5 sentence that we just read that there's a 6 reference there to the IARC publication in 2010. 7 We've already discussed that, correct? 8 A Yes. 9 Q And then there's a reference to 10 subsequent evaluations by individual 11 investigators, and there's a reference there to 12 articles or studies 3, 5 and 69. Do you see that? 13 A I see that. 14 Q And looking at the reference pages, 15 beginning on page 51, would you agree that 16 reference 3 is the Berge analysis, this citation 17 is to 2017, correct? 18 A Correct. 19 Q Five is Penninkilampi, correct? 20 A Correct. 21 Q And the last reference, which is 69, is 22 to the Terry meta-analysis. Do you see that? 23 A Terry is not a meta-analysis. It's a 24 pooled analysis. But I see that, yes. 25 Q Okay. So the reference in the Taher</p>	<p style="text-align: right;">Page 240</p> <p>1 Q And that they examined those studies 2 closely enough at least to reach the conclusion in 3 their own mind that their results were consistent 4 with those findings. 5 MS. PARFITT: Objection. Form. 6 THE WITNESS: Yes. 7 BY MS. BRANSCOME: 8 Q Are there any scientific publications 9 that were available to you during your review in 10 connection with your formation of opinions in the 11 MDL that were not available to the authors of the 12 Taher manuscript? 13 MS. PARFITT: Objection. Form. 14 THE WITNESS: So are you talking about 15 the meta-analysis that -- are you talking about 16 studies that went into meta-analysis or are you 17 talking about the, you know, 200 or 300 references 18 in my bibliography? 19 BY MS. BRANSCOME: 20 Q Fair enough. 21 Are there any studies that you included 22 in your meta-analysis that, at least to your 23 knowledge, were available to you and were not 24 available to the Taher authors? 25 MS. PARFITT: Objection. Form.</p>
<p style="text-align: right;">Page 239</p> <p>1 manuscript to reference 69 is to the Terry pooled 2 analysis from 2013, correct? 3 A Correct. 4 Q And so you agree that at least the Taher 5 authors considered the Berge, Penninkilampi, and 6 Terry studies. 7 MS. PARFITT: Objection. Form. 8 THE WITNESS: Were aware of. I'm not 9 sure what you mean by considered. They -- they 10 referenced it. I don't know that they considered 11 it in their -- I don't imagine that there's any 12 place in their statistical analysis where they 13 introduced data from any of those papers. They're 14 just acknowledging that those other meta-analyses 15 found the same thing that they found. 16 BY MS. BRANSCOME: 17 Q So perhaps we have a different 18 understanding of the word "considered." 19 A Okay. 20 Q Would you agree that a fair reading of 21 their Conclusion paragraph would indicate that the 22 Taher authors were first aware -- 23 A Yes. 24 Q -- of Terry, Berge and Penninkilampi? 25 A Yes.</p>	<p style="text-align: right;">Page 241</p> <p>1 THE WITNESS: Oh, they would have been 2 available because all of my -- the studies I used 3 are in publicly available literature, and I'm sure 4 they were available. 5 BY MS. BRANSCOME: 6 Q Okay. Do you have any criticisms of the 7 Taher 2018 meta-analysis? 8 A I haven't evaluated it closely enough 9 to -- to formulate criticisms or praise or -- 10 Q Now, you testified earlier that there 11 was a flurry of activity in December surrounding 12 the information from Health Canada and the Taher 13 manuscript. 14 Is there a reason why you have not 15 reviewed the Taher manuscript in detail and formed 16 an opinion about whether you agree or disagree 17 with its analysis? 18 MS. PARFITT: Objection. Fully 19 misstates his testimony. Form. 20 THE WITNESS: I -- I thought that it 21 would have absolutely no bearing on the results 22 and the opinions that I expressed in my report, 23 plus I didn't have time to do such a review. And 24 so the combination of those two things made it a 25 simple decision not to devote precious time and</p>

<p style="text-align: right;">Page 242</p> <p>1 effort to a -- a futile activity.</p> <p>2 I'm not uninterested in what they did or</p> <p>3 what they found, but I can predict pretty quickly</p> <p>4 what they did and what they found, and I -- I know</p> <p>5 the studies that they reviewed, that they had</p> <p>6 access to. There's nothing that they would find</p> <p>7 that I wouldn't be able to predict.</p> <p>8 MS. BRANSCOME: Okay.</p> <p>9 Now may be a good time to take a break.</p> <p>10 MS. PARFITT: Sure. Okay. Very good.</p> <p>11 MS. BRANSCOME: Let's go off the record.</p> <p>12 MR. TISI: Are we switching examiners</p> <p>13 too?</p> <p>14 MS. BRANSCOME: I don't know. That's</p> <p>15 why --</p> <p>16 MS. PARFITT: Oh, fair enough. Fair</p> <p>17 enough.</p> <p>18 THE VIDEOGRAPHER: We're going off the</p> <p>19 record at 6:22 p.m.</p> <p>20 (Recess.)</p> <p>21 THE VIDEOGRAPHER: This begins disc</p> <p>22 number 5 in the deposition of Jack Siemiatycki.</p> <p>23 We are going back on the record at 6:40 p.m.</p> <p>24 BY MS. BRANSCOME:</p> <p>25 Q So, Dr. Siemiatycki, if you could open</p>	<p style="text-align: right;">Page 244</p> <p>1 criteria, but which are not criteria and shouldn't</p> <p>2 be called criteria.</p> <p>3 Q Understanding that you have specific</p> <p>4 views about the appropriateness and application of</p> <p>5 it, you are at least familiar with what is</p> <p>6 sometimes referred to as a Bradford Hill analysis</p> <p>7 or the Hill criteria, correct?</p> <p>8 A I don't -- again, the phrase "Bradford</p> <p>9 Hill analysis" doesn't mean anything. I don't</p> <p>10 think you would find that phrase in any</p> <p>11 epidemiology or statistics textbook.</p> <p>12 Q Are you saying as you sit here today,</p> <p>13 Dr. Siemiatycki, you've never heard of the Hill</p> <p>14 criteria?</p> <p>15 MS. PARFITT: Objection. Misstates his</p> <p>16 testimony.</p> <p>17 THE WITNESS: No, I've heard of it, and</p> <p>18 I'm saying that it's a misnomer. And so I'd</p> <p>19 prefer if the correct terminology is used when --</p> <p>20 if you're asking me questions about it.</p> <p>21 BY MS. BRANSCOME:</p> <p>22 Q The authors of the Taher manuscript use</p> <p>23 the term "Hill criteria" --</p> <p>24 A Yes.</p> <p>25 Q -- in their Table 2, correct?</p>
<p style="text-align: right;">Page 243</p> <p>1 back up to the Taher manuscript again. I believe</p> <p>2 it's in your binder that's been marked as</p> <p>3 Exhibit 6, and specifically, if you could go to</p> <p>4 Figure 3 on page 39.</p> <p>5 Have you looked at Figure 3 from the</p> <p>6 Taher 2018 manuscript before now?</p> <p>7 A No, I haven't. I may have glanced at it</p> <p>8 going through it, but I haven't examined it.</p> <p>9 Q Did you look at anything in the Taher</p> <p>10 manuscript to support your opinion that there is</p> <p>11 at least evidence compatible with the dose-</p> <p>12 response relationship between perineal use of talc</p> <p>13 and ovarian cancer?</p> <p>14 A I didn't look for that in this paper.</p> <p>15 Q If you could look at page 25 of the</p> <p>16 Taher paper.</p> <p>17 Do you see here that the authors of the</p> <p>18 Taher manuscript describe the summary of evidence</p> <p>19 for each of the Hill criteria of causation? Do</p> <p>20 you see that?</p> <p>21 A I see that.</p> <p>22 Q And you are familiar with the Hill --</p> <p>23 the Hill criteria of causation, correct?</p> <p>24 A I'm familiar with what they call the</p> <p>25 Hill criteria and what some people call the Hill</p>	<p style="text-align: right;">Page 245</p> <p>1 A Yes, they do.</p> <p>2 Q And there is a discussion under the --</p> <p>3 what they refer to as a criterion for strength of</p> <p>4 association, correct?</p> <p>5 A Yes.</p> <p>6 Q And the Taher authors report that out of</p> <p>7 30 epidemiological studies --</p> <p>8 it's late in the day -- six reported positive</p> <p>9 association of statistical significance with a</p> <p>10 risk value, relative risk or odds ratio of 1.5 or</p> <p>11 greater.</p> <p>12 Is that description of the</p> <p>13 epidemiological studies accurate?</p> <p>14 A I don't know. I haven't counted. I</p> <p>15 haven't done that kind of counting, which is</p> <p>16 irrelevant and wrong from a statistical and</p> <p>17 epidemiological point of view to do it. So I</p> <p>18 haven't done it, and I can't confirm that there</p> <p>19 are six that report odds ratios greater than 1.5.</p> <p>20 I could do that if you want me to. I can look</p> <p>21 through studies and see.</p> <p>22 But there's no -- there's no scientific</p> <p>23 purpose in doing that. It's a meaningless piece</p> <p>24 of information.</p> <p>25 Q Would you criticize the Taher authors</p>

<p style="text-align: right;">Page 246</p> <p>1 for their discussion of the Hill criteria?</p> <p>2 A Yes.</p> <p>3 Q And you have explained your criticisms</p> <p>4 about the Hill criteria in both your trial</p> <p>5 testimony and in your prior deposition testimony,</p> <p>6 correct?</p> <p>7 A I can't remember the details, but I -- I</p> <p>8 guess if I was asked about it, I explained what I</p> <p>9 thought about it.</p> <p>10 My criticism -- I'm not sure what you</p> <p>11 mean by my criticisms of the term or of the</p> <p>12 concepts that the paper that Hill wrote in 1965,</p> <p>13 the ways -- the umpteen different ways that other</p> <p>14 people have interpreted it. What -- what are you</p> <p>15 referring to when you say I criticized? What did</p> <p>16 I criticize?</p> <p>17 Q Have your views with respect to the use</p> <p>18 and application of the so-called Hill criterion</p> <p>19 changed since you testified in the Echeverria</p> <p>20 trial?</p> <p>21 MS. PARFITT: Objection. Form.</p> <p>22 THE WITNESS: They -- they haven't</p> <p>23 changed in 40 years.</p> <p>24 BY MS. BRANSCOME:</p> <p>25 Q Okay. Thank you.</p>	<p style="text-align: right;">Page 248</p> <p>1 Q 48 in my binder, but I don't know if you</p> <p>2 have a copy in yours, which might be faster.</p> <p>3 A No, this -- I have the -- I have the</p> <p>4 current Berge paper. So...</p> <p>5 Q At page 9, I believe.</p> <p>6 Well, that's confusing to say page 9.</p> <p>7 A Okay, I see that.</p> <p>8 Q Okay. In reviewing the conclusion that</p> <p>9 the Berge authors reached, would -- did the Berge</p> <p>10 authors conclude that genital talc use was a</p> <p>11 probable cause of ovarian cancer?</p> <p>12 A They did not indicate that they</p> <p>13 concluded that.</p> <p>14 Q Okay. And same for the Penninkilampi</p> <p>15 study.</p> <p>16 MS. PARFITT: Had you finished? Had you</p> <p>17 finished your statement.</p> <p>18 THE WITNESS: Not quite.</p> <p>19 There's a difference between the</p> <p>20 findings of a study and the inferences that are</p> <p>21 drawn from those findings. So the findings of</p> <p>22 their meta-analyses and the findings of the</p> <p>23 Penninkilampi meta-analyses and findings of the</p> <p>24 Taher meta-analyses are the same as my findings.</p> <p>25 All four agree on the findings.</p>
<p style="text-align: right;">Page 247</p> <p>1 Now, we have just discussed three</p> <p>2 meta-analyses: The Berge meta-analyses, the</p> <p>3 Penninkilampi meta-analyses, and the Taher</p> <p>4 meta-analyses. Correct?</p> <p>5 A Yes.</p> <p>6 Q Would you agree that none of the authors</p> <p>7 of those three meta-analyses concluded that talc</p> <p>8 was a probable cause of ovarian cancer?</p> <p>9 MS. PARFITT: Objection. Form.</p> <p>10 THE WITNESS: The purpose of those</p> <p>11 meta-analyses was to estimate the meta-estimate of</p> <p>12 relative risk. In terms of the conclusion about</p> <p>13 probable causation, I think they all commented on</p> <p>14 it in their discussions.</p> <p>15 And can you specify your question again,</p> <p>16 whether they concluded that it was a probable</p> <p>17 cause?</p> <p>18 BY MS. BRANSCOME:</p> <p>19 Q Correct.</p> <p>20 A I'd have to look at the way they -- what</p> <p>21 conclusions they drew, I'd have to look at that.</p> <p>22 Q Okay. If we could look at the Berge</p> <p>23 paper, which should be tab --</p> <p>24 A Let me see, I think I have the latest</p> <p>25 issue of the Berge paper.</p>	<p style="text-align: right;">Page 249</p> <p>1 Interpreting and making inferences is a</p> <p>2 whole other bailiwick, a whole other activity, and</p> <p>3 they don't -- didn't conclude in this section that</p> <p>4 it's a probable cause. From the same evidence, I</p> <p>5 do conclude that it's a probable cause.</p> <p>6 BY MS. BRANSCOME:</p> <p>7 Q Right. And the same is true for the</p> <p>8 Penninkilampi officer -- authors, correct?</p> <p>9 A Sorry, I have to go through it.</p> <p>10 (Peruses document.)</p> <p>11 I don't really agree with your</p> <p>12 statement. I don't think they conclude that it's</p> <p>13 probable or not probable. I don't see -- can you</p> <p>14 point me to a statement that would imply that it's</p> <p>15 not -- that they think it's not probable?</p> <p>16 Q Do the authors of the Penninkilampi</p> <p>17 paper use the phrase, quote, suggestive of a</p> <p>18 causal association, in the Conclusion section?</p> <p>19 A Yes, they do.</p> <p>20 Q Okay. Would you say that "suggestive of</p> <p>21 a causal association" is equivalent to probable</p> <p>22 causation?</p> <p>23 MS. PARFITT: Objection. Form.</p> <p>24 THE WITNESS: That's a semantic</p> <p>25 question, and how different people and different</p>

<p style="text-align: right;">Page 250</p> <p>1 cultures -- and I think these people are  2 Australians -- how Australians tend to use the  3 word "suggestive." I -- I don't read this in a  4 way as to suggest that they don't think it's  5 probable.  6 BY MS. BRANSCOME:  7 Q So you don't know from reviewing the  8 Conclusion section one way or the other whether  9 the Penninkilampi authors view perineal use of  10 talc as a probable cause of ovarian cancer.  11 MS. PARFITT: Objection. Form,  12 misstates his testimony.  13 Just answer the question.  14 THE WITNESS: Yes, that's right, I -- I  15 don't.  16 BY MS. BRANSCOME:  17 Q Okay. And as we just looked at in the  18 Taher manuscript, the Taher authors describe that  19 the data indicates perineal exposure to talc  20 powder is a possible cause of ovarian cancer in  21 humans, correct?  22 And if you need the reference, it's  23 page 49.  24 A That's correct.  25 Possible does not preclude probable, by</p>	<p style="text-align: right;">Page 252</p> <p>1 "possible" here can cover a range of possibilities  2 that includes probable.  3 So if something is possible, that means  4 it could happen, and in their view or in some of  5 their -- those authors' view, the possibility or  6 the probability of -- of such a thing happening  7 might be greater than 50 percent, and they might  8 still describe it as a possible cause of ovarian  9 cancer.  10 Q You would be --  11 MR. KLATT: Object. Nonresponsive.  12 Sorry.  13 BY MS. BRANSCOME:  14 Q You would be purely speculating to opine  15 that the Taher authors, for example, when they  16 used the term "possible" to describe the  17 association, they actually meant probable,  18 correct?  19 MS. PARFITT: Objection. Form.  20 THE WITNESS: I didn't say they -- they  21 actually -- I meant -- I said that it could  22 include probable.  23 And so you are -- the sense of your  24 question is to suppose or assume that their use of  25 the word "possible" excludes the concept of</p>
<p style="text-align: right;">Page 251</p> <p>1 the way. I'm not -- I'm not assume- -- are you  2 assuming that they had in mind the IARC  3 classification system and that these two  4 categories are mutually exclusive?  5 Q My question to you, Dr. Siemiatycki, is  6 did any of the authors of the three other  7 meta-analyses, Berge, Penninkilampi or Taher,  8 conclude in their papers that perineal talc use is  9 a probable cause of ovarian cancer?  10 MS. PARFITT: Objection. Form. Asked  11 and answered.  12 THE WITNESS: They did not use that  13 word. But I would not infer that they don't think  14 it's a probable cause from the write-up of  15 their -- from their write-up. It is possible that  16 they consider the description of this as a --  17 where is the word "possible"? Is that in the  18 Conclusion?  19 BY MS. BRANSCOME:  20 Q It is.  21 A Oh, yeah, possible cause.  22 You know, they are -- I mean, I can't  23 speak for them because I haven't spoken to any of  24 them about this, but I don't think they're  25 speaking to a legal audience. And the word</p>	<p style="text-align: right;">Page 253</p> <p>1 probable, that they did not think it's -- because  2 they used the word "possible," they absolutely  3 denied that it's probable. And I -- that's what  4 I'm disagreeing with.  5 BY MS. BRANSCOME:  6 Q Where I'm coming from is not relevant to  7 the question that I'm asking, Dr. Siemiatycki.  8 The question that I'm asking you is, do any of the  9 authors of the three meta-analyses that we just  10 reviewed, Berge, Penninkilampi, and Taher,  11 describe in their papers the association between  12 perineal use of talc and ovarian cancer as a  13 probable causal association?  14 MS. PARFITT: Objection. Form.  15 BY MS. BRANSCOME:  16 Q Do any of them use that term?  17 MS. PARFITT: Objection. Form.  18 THE WITNESS: None of them use that  19 term, but that doesn't preclude that they -- some  20 of them believe it is probable.  21 MR. KLATT: Object. Nonresponsive.  22 BY MS. BRANSCOME:  23 Q You have no basis for concluding or even  24 suggesting that any of these authors have the  25 opinion that it is a probable causal association</p>

<p style="text-align: right;">Page 254</p> <p>1 other than speculating based off of what you're  2 reading on the page, correct?  3 MS. PARFITT: Objection. Form.  4 THE WITNESS: Correct. Nor do I have  5 any basis for assuming that they don't think it's  6 probable on the basis of what I read.  7 BY MS. BRANSCOME:  8 Q When you write scientific manuscripts,  9 Dr. Siemiatycki, are you careful about your word  10 choice, particularly in your conclusion section?  11 MS. PARFITT: Objection. Form.  12 THE WITNESS: I try to be. I try to be.  13 BY MS. BRANSCOME:  14 Q Okay. If you could turn to tab 33 in  15 your binder.  16 Are you familiar with the document that  17 is located behind tab 33 in your binder there?  18 A I -- I think so. I -- mine had a  19 different cover page when I printed it off, but  20 that's fine. I'm -- I assume it's the same one  21 I -- I had.  22 MR. TISI: It's not. It's not.  23 MS. PARFITT: What are you referring to?  24 MR. TISI: The draft article is not --  25 MS. PARFITT: Yeah, I know that.</p>	<p style="text-align: right;">Page 256</p> <p>1 bureau or division. I'm not quite sure.  2 Q Okay. And the document that you're  3 looking at there is contained within a binder that  4 we have previously marked as Exhibit 4, correct?  5 A Correct.  6 Q All right. Is this an item -- is this  7 an item.  8 Is this Draft Screening Assessment a  9 document that you considered in forming your  10 opinions in this case?  11 A No, it isn't.  12 Q Why not?  13 A Because I was only aware of it a month  14 or -- a month and a half or two months after I  15 completed my report, and two years after I formed  16 the main part of my opinion.  17 Q How did you obtain a copy of the Draft  18 Screening Assessment by Health Canada?  19 A I think that this was on the internet.  20 I think I --  21 THE WITNESS: Yeah, some other -- there  22 should be a light button that we can press.  23 Excuse me. Excuse me, just maybe off  24 the record for a second.  25 (A discussion was held off the record.)</p>
<p style="text-align: right;">Page 255</p> <p>1 THE WITNESS: Is it the Draft Screening  2 Assessment?  3 MR. TISI: No, that's not the same.  4 THE WITNESS: No?  5 MR. TISI: It's not.  6 MS. PARFITT: Do you have a copy of  7 yours?  8 THE WITNESS: Yeah.  9 MS. BRANSCOME: Can we go off the record  10 while we figure this out?  11 MS. PARFITT: Sure, that would be fine.  12 THE VIDEOGRAPHER: We're going off the  13 record at 6:58 p.m.  14 (Pause in the proceedings.)  15 THE VIDEOGRAPHER: We're back on the  16 record at 7:01 p.m.  17 BY MS. BRANSCOME:  18 Q Dr. Siemiatycki, you have a document in  19 front of you that is labeled a "Draft Screening  20 Assessment" dated December 2018; is that correct?  21 A Yes, I do.  22 Q And this is a screening assessment by  23 the Environment and Climate Change Canada, Health  24 Canada, correct?  25 A It's a branch of Health Canada or a</p>	<p style="text-align: right;">Page 257</p> <p>1 THE VIDEOGRAPHER: We are going off the  2 record at 7:03 p.m.  3 (Pause in the proceedings.)  4 THE VIDEOGRAPHER: We are back on the  5 record at 7:03 p.m.  6 BY MS. BRANSCOME:  7 Q Dr. Siemiatycki, we paused because the  8 lights turned off, but my question to you is, how  9 did you obtain a copy of the Draft Screening  10 Assessment by Health Canada?  11 A Either it was sent to me by Ms. Parfitt  12 or her staff, or I found it on the internet. And  13 I can't quite remember now.  14 Q Do you remember when you first obtained  15 a copy of the Draft Screening Assessment?  16 A My guess is just before I went on  17 vacation for Christmas and New Years. So it would  18 have been mid -- mid to -- mid-December, I guess,  19 something like that.  20 Q Are you familiar with the process by  21 which draft screening assessments are generated by  22 Health Canada?  23 A No, not really. I was involved with  24 this department of Health Canada 30 years ago, and  25 I haven't been involved since. I don't know how</p>

<p style="text-align: right;">Page 258</p> <p>1 they function really to produce these evaluations</p> <p>2 and reports.</p> <p>3 Q Did you have any involvement, even</p> <p>4 tangentially, in the development of the Draft</p> <p>5 Screening Assessment by Health Canada?</p> <p>6 A No.</p> <p>7 Q Were you ever asked to consult on any of</p> <p>8 the content that ultimately ended up in the Draft</p> <p>9 Screening Assessment?</p> <p>10 A No, I wasn't.</p> <p>11 Q Were you ever contacted about</p> <p>12 potentially being involved in a Draft Screening</p> <p>13 Assessment of talc for Health Canada?</p> <p>14 A No. Never.</p> <p>15 Q You are aware that this is in fact a</p> <p>16 draft assessment by Health Canada, correct?</p> <p>17 MS. PARFITT: Objection. Form.</p> <p>18 THE WITNESS: I see that's what it says</p> <p>19 on the cover page.</p> <p>20 BY MS. BRANSCOME:</p> <p>21 Q Are you aware of what further steps in</p> <p>22 the process must be taken before the draft</p> <p>23 assessment is potentially accepted or modified?</p> <p>24 MS. PARFITT: Objection. Form.</p> <p>25 THE WITNESS: I'm not familiar with the</p>	<p style="text-align: right;">Page 260</p> <p>1 A Yes.</p> <p>2 Q Do you believe --</p> <p>3 A If I make such a submission, yes.</p> <p>4 Q Why -- well, first of all, do you think</p> <p>5 it's important to disclose your involvement in the</p> <p>6 litigation if you were to submit something for</p> <p>7 public comment?</p> <p>8 A Yes, I think it is.</p> <p>9 Q And why is that?</p> <p>10 A Because there's a potential conflict of</p> <p>11 interest, and they should know about it.</p> <p>12 Q Would you also notify IARC of your role</p> <p>13 in litigation involving talcum powder products if</p> <p>14 you submitted something to them to suggest that a</p> <p>15 formal evaluation of talc be conducted?</p> <p>16 A Yes, I would.</p> <p>17 Q Is that for the same reason?</p> <p>18 A Yes, it is.</p> <p>19 Q Is the Draft Screening Assessment the</p> <p>20 type of material that you think it is reliable to</p> <p>21 base an expert opinion on?</p> <p>22 MS. PARFITT: Objection. Form.</p> <p>23 THE WITNESS: An expert opinion about</p> <p>24 what?</p> <p>25 BY MS. BRANSCOME:</p>
<p style="text-align: right;">Page 259</p> <p>1 details, no.</p> <p>2 BY MS. BRANSCOME:</p> <p>3 Q What are you familiar with, if not the</p> <p>4 details?</p> <p>5 A I remember seeing that there's a public</p> <p>6 consultation opportunity, and -- so I guess there</p> <p>7 will be a period of time during which they will</p> <p>8 accept public recommendations and comments. And I</p> <p>9 don't know if it's the same committee that will</p> <p>10 then review all of that or a committee that's</p> <p>11 higher up on the administrative pecking order. I</p> <p>12 don't -- I don't know what happens internally.</p> <p>13 Q Do you intend to submit anything for</p> <p>14 the -- during the public comment period?</p> <p>15 A I -- yeah, I hope to do so. I hope to</p> <p>16 do so.</p> <p>17 Q What specifically do you intend to</p> <p>18 submit?</p> <p>19 A I'm not sure yet. I -- I would probably</p> <p>20 submit an opinion supporting the notion that</p> <p>21 perineal use of talc is more likely than not</p> <p>22 related to ovarian cancer.</p> <p>23 Q In your submission, do you intend to</p> <p>24 disclose your role in litigation involving talcum</p> <p>25 powder products?</p>	<p style="text-align: right;">Page 261</p> <p>1 Q About the potential relationship between</p> <p>2 talc and ovarian cancer.</p> <p>3 MS. PARFITT: Objection. Form.</p> <p>4 THE WITNESS: Are you asking if it would</p> <p>5 influence my opinion on the issue or --</p> <p>6 BY MS. BRANSCOME:</p> <p>7 Q So under- -- understanding that the</p> <p>8 Draft Screening Assessment came out after you had</p> <p>9 formed your opinion, I'm asking you that if that</p> <p>10 had not been the case, if it had come out while</p> <p>11 you were still forming your expert opinion, is</p> <p>12 this something that you would rely on?</p> <p>13 A I would take cognizance of it, and I'm</p> <p>14 not sure whether it would persuade me in one</p> <p>15 direction or another on the strength of the</p> <p>16 evidence, but it -- it would certainly give me --</p> <p>17 increase my comfort level to draw inferences to</p> <p>18 see what inferences other people draw. I won't</p> <p>19 necessarily follow their opinions, but I find it</p> <p>20 useful to know what inferences they would draw</p> <p>21 from it.</p> <p>22 Q Is a Draft Screening Assessment the type</p> <p>23 of report or publication that you see cited in</p> <p>24 published scientific literature?</p> <p>25 MS. PARFITT: Objection. Form.</p>

<p style="text-align: right;">Page 262</p> <p>1 THE WITNESS: Not -- not -- in 2 scientific literature, not so much, no. 3 BY MS. BRANSCOME: 4 Q The draft assessment -- first of all, 5 are you familiar with the proposal with respect to 6 talc that's contained in the draft assessment? 7 A Which proposal are you referring to? 8 Q I could refer you specifically to 9 page -- 10 MR. TISI: I spilled coffee on it too. 11 Sorry. You get what you get. 12 BY MS. BRANSCOME: 13 Q -- on page 29. 14 A The Conclusion section? 15 Q Yes. Have you reviewed this before? 16 A I -- I might have looked at it quickly. 17 But let me -- let me review it -- let me read it 18 now. (Peruses document.) 19 You know, it refers to the fit of the -- 20 their findings and conclusions with various 21 articles of law in the Canadian Environmental 22 Protection Act. I would have to know what those 23 articles of law are that this conforms to, that 24 these sentences purportedly conform to. I -- I 25 have no reason to doubt what they say, but I -- I</p>	<p style="text-align: right;">Page 264</p> <p>1 describing the conclusion as a proposal? Or -- 2 yeah. 3 BY MS. BRANSCOME: 4 Q Focusing specifically on the second 5 paragraph where it says: "It is proposed to 6 conclude that talc meets the criteria under 7 paragraph 64(c) of CEPA as it is entering or may 8 enter the environment in a quantity or 9 concentration or under conditions that constitute 10 or may constitute a danger in Canada to human life 11 or health." 12 MS. PARFITT: Objection. Form. 13 THE WITNESS: It's not a way of 14 describing scientific evidence that I'm intimately 15 familiar with. So I would need to review this 16 document in more detail and be aware of the 17 paragraph 64(c) of the CEPA. 18 BY MS. BRANSCOME: 19 Q And that is not something you -- 20 A So I'm not -- 21 Q -- have done as of today? 22 A It's not something I base -- today I 23 couldn't say I agree with this or I don't agree 24 with this. 25 Q Okay. And so this is not -- the Draft</p>
<p style="text-align: right;">Page 263</p> <p>1 can't confirm. 2 Q So as you sit here today, are you 3 capable or prepared to offer an opinion as to how 4 the conclusions in the Draft Screening Assessment 5 relate to other pieces of literature that we've 6 discussed today? 7 MS. PARFITT: Objection. Form. 8 THE WITNESS: How they relate to -- or 9 whether they're concordant with other pieces? 10 It's difficult for me to say without studying this 11 document more and seeing what the conformity is 12 with the Canadian pieces of legislation that they 13 refer to. So I -- I can't -- I can't give you 14 much more than that. 15 BY MS. BRANSCOME: 16 Q So as you sit here today, could you -- 17 do you have an opinion as to how the proposal in 18 the Draft Screening Assessment with respect to 19 talc relates to the current IARC classification of 20 talc? 21 MS. PARFITT: Objection. Form. 22 THE WITNESS: By proposal, you mean the 23 conclusion? 24 MS. PARFITT: The entire document. 25 THE WITNESS: You're -- you're</p>	<p style="text-align: right;">Page 265</p> <p>1 Screening Assessment by Health Canada is not 2 something that you are relying upon in any way in 3 offering your expert opinions in this case; is 4 that correct? 5 MS. PARFITT: Objection. Form, 6 misstates his testimony. 7 THE WITNESS: No. As I said, I didn't 8 rely on this to form my opinion. 9 BY MS. BRANSCOME: 10 Q Okay. 11 MS. BRANSCOME: Could we go off the 12 record just briefly? 13 MS. PARFITT: Of course. 14 THE VIDEOGRAPHER: We're going off the 15 record at 7:15 p.m. 16 (Pause in the proceedings.) 17 THE VIDEOGRAPHER: We're back on the 18 record at 7:16 p.m. 19 BY MS. BRANSCOME: 20 Q Dr. Siemiatycki, can you describe -- can 21 you identify for me specifically the pieces of 22 evidence that you would cite to in support of your 23 opinion that there is evidence consistent with a 24 dose-response relationship that was not considered 25 by the IARC 2006 working group?</p>

<p style="text-align: right;">Page 266</p> <p>1 A Can --</p> <p>2 Q And I'm just looking for an</p> <p>3 identification of the papers.</p> <p>4 A Let me just dig out -- I keep hiding</p> <p>5 things from myself.</p> <p>6 MS. PARFITT: Okay.</p> <p>7 THE WITNESS: Oh, there.</p> <p>8 The primary pieces of evidence -- the</p> <p>9 primary piece of evidence is the analysis carried</p> <p>10 out in the Terry, et al., paper where they</p> <p>11 combined ten different studies from eight</p> <p>12 different research teams. They had by far the</p> <p>13 largest sample size of any conglomeration of</p> <p>14 studies ever conducted, enough to properly</p> <p>15 evaluate dose-response. And that's one of them.</p> <p>16 The second one is the Schildkraut study,</p> <p>17 which is much smaller than the Terry study in</p> <p>18 terms of numbers.</p> <p>19 And the third -- a third one, which was</p> <p>20 not part of the evidence that influenced my</p> <p>21 evaluation, is the latest version of the Berge</p> <p>22 paper which has some dose-response results in a</p> <p>23 table whose origin I don't completely understand,</p> <p>24 but ostensibly it gives dose-response trends that</p> <p>25 are significant and meaningful for duration and</p>	<p style="text-align: right;">Page 268</p> <p>1 use your own copy if that's more convenient.</p> <p>2 A Yep. There we go. Okay.</p> <p>3 Q Did the authors of the Terry 2013 paper,</p> <p>4 did they conclude in their manuscript that they</p> <p>5 had observed a statistically significant dose-</p> <p>6 response relationship between the perineal use of</p> <p>7 talc and ovarian cancer?</p> <p>8 A They reported two different ways of</p> <p>9 calculating the statistical significance of a</p> <p>10 trend. One of them was significant, and the other</p> <p>11 was formal, in terms of the conventional 0.05</p> <p>12 statistical significance level, was not</p> <p>13 significant at that level.</p> <p>14 Q And in fact in the abstract, the authors</p> <p>15 of the Terry paper state that: "Among genital</p> <p>16 powder users, we observed no significant trend,</p> <p>17 p equals 0.17, in risk with increasing number of</p> <p>18 lifetime applications," in parentheses, "assessed</p> <p>19 in quartiles."</p> <p>20 Did I read that correctly?</p> <p>21 A That's correct.</p> <p>22 Q Okay. Now, in your 2016 report --</p> <p>23 A Yeah.</p> <p>24 Q -- you had the statement that: "The</p> <p>25 appropriate statistical test for trend is one that</p>
<p style="text-align: right;">Page 267</p> <p>1 frequency of exposure. But I would put less</p> <p>2 weight on that until I fully understand what --</p> <p>3 how they derived those estimates.</p> <p>4 BY MS. BRANSCOME:</p> <p>5 Q Okay. So the pieces of evidence that</p> <p>6 you would cite to in support of the idea that</p> <p>7 there has been a development that is supportive of</p> <p>8 a dose-response relationship between perineal talc</p> <p>9 and ovarian cancer since the IARC classification</p> <p>10 of talc as a 2B would be the Terry, the</p> <p>11 Schildkraut, and potentially the Berge analysis;</p> <p>12 is that correct?</p> <p>13 MS. PARFITT: Objection --</p> <p>14 THE WITNESS: Yes.</p> <p>15 MS. PARFITT: -- to the reference of</p> <p>16 "potentially the Berge." Form.</p> <p>17 BY MS. BRANSCOME:</p> <p>18 Q You did not rely in any way on the</p> <p>19 analysis in the Berge 2018 paper for your</p> <p>20 conclusion that there is evidence compatible with</p> <p>21 a dose-response relationship between perineal talc</p> <p>22 use and ovarian cancer, correct?</p> <p>23 A That's correct.</p> <p>24 Q Okay. So looking first at the Terry</p> <p>25 2013 paper. This is tab 14 or you're welcome to</p>	<p style="text-align: right;">Page 269</p> <p>1 excludes the baseline unexposed category."</p> <p>2 Do you remember having that sentence in</p> <p>3 your 2016 report?</p> <p>4 A I remember the -- the idea being there,</p> <p>5 yes.</p> <p>6 Q Okay. And you would agree that if you</p> <p>7 apply that statistical test for trend, meaning you</p> <p>8 exclude the baseline unexposed category, the Terry</p> <p>9 2013 paper does not demonstrate a dose-response</p> <p>10 relationship, correct?</p> <p>11 MS. PARFITT: Objection.</p> <p>12 THE WITNESS: No.</p> <p>13 MS. PARFITT: Misstates testimony.</p> <p>14 THE WITNESS: So I would not conclude --</p> <p>15 I would say that it demonstrates dose-response,</p> <p>16 but not at a statistical -- at a 0.05 statistical</p> <p>17 significance level.</p> <p>18 And I would also -- I can't remember the</p> <p>19 wording and the context in the 2016 report that</p> <p>20 you're referring to, but I would imagine that I</p> <p>21 preceded that statement with some mention of the</p> <p>22 fact that it depends if you are using the overall</p> <p>23 risk among all exposed people compared to</p> <p>24 unexposed people as a complementary piece of</p> <p>25 information.</p>

<p style="text-align: right;">Page 270</p> <p>1 And it's only in the context when you 2 are using the -- all the exposed compared to all 3 the unexposed, and at the same time carrying out 4 an analysis of the different levels of exposure, 5 that including the unexposed among the -- in that 6 trend analysis becomes overlapping information 7 with the overall -- the significance of the 8 overall estimate. 9 BY MS. BRANSCOME: 10 Q Okay. 11 A This -- I'm not quite finished. Sorry. 12 So -- and because I don't want you to 13 think that I believe or believed that on its own 14 there is no evidence of dose-response. There is 15 evidence of dose-response in the Terry analysis. 16 The choice of which p-value to report on the trend 17 analysis depends completely on how one combines 18 that information with the ever exposed/never 19 exposed information and the p-value for that. 20 That when we want completely independent and 21 separate strands of evidence to corroborate each 22 other, then it's appropriate to exclude the 23 unexposed from the p-value computation. 24 When you are using -- when you are not 25 using the binary exposed/unexposed as part of the</p>	<p style="text-align: right;">Page 272</p> <p>1 are you positing? 2 BY MS. BRANSCOME: 3 Q Of those ten studies, which, if any of 4 them, postdate 2006? Do you know? 5 A Most of them do. I would say -- I think 6 the only one -- ones that were published before 7 2006 were a study by Chang and one or two of the 8 components of Cramer's studies. I think the rest 9 were all published post-2006. 10 Q Okay. Did you independently do an 11 analysis of the potential dose-response 12 relationship of perineal talc use and ovarian 13 cancer? 14 MS. PARFITT: Objection. Form. 15 THE WITNESS: By "independently," you 16 mean trying to replicate the Terry analysis? No. 17 I don't see why I would be motivated to do 18 something that someone else has already done. 19 BY MS. BRANSCOME: 20 Q Okay. So you are relying on the data as 21 reported by Terry 2013 that you consider to be 22 evidence in support of a dose-response 23 relationship, correct? 24 A That's correct. 25 Q Okay. But the authors themselves do not</p>
<p style="text-align: right;">Page 271</p> <p>1 package of information to demonstrate causation, 2 then the correct p-value is the one that includes 3 the unexposed. So it depends how you use these 4 things. 5 If I didn't qualify that statement that 6 you read before, then I was in error. 7 Q If you did not have the Terry 2013 8 study -- 9 A Yes. 10 Q -- set that aside for a moment, you did 11 not have that data, would it still be your opinion 12 that the perineal use of talc probably causes 13 ovarian cancer? 14 A So -- 15 MS. PARFITT: Objection. Form. 16 THE WITNESS: So just to be clear what 17 the hypothetical supposition is, so the Terry 18 paper doesn't exist, but the studies underlying 19 the Terry paper still do exist, correct? Or they 20 don't exist either? 21 So there are ten studies underlying the 22 Terry reanalysis. Is your hypothetical question 23 about the possibility that none of those studies 24 existed or that they existed, but nobody actually 25 put them together to combine an analysis? What</p>	<p style="text-align: right;">Page 273</p> <p>1 conclude that there has been a statistically 2 significant dose-response relationship established 3 for the perineal use of talc and ovarian cancer, 4 correct? 5 MS. PARFITT: Objection. Form, 6 misstates the evidence. 7 THE WITNESS: I -- I didn't review what 8 they concluded in the Discussion section. If you 9 want, I could review that. And I -- I don't 10 remember what -- what kind of narrative inferences 11 they made about it. 12 BY MS. BRANSCOME: 13 Q Okay. 14 A You're asking me to confirm that they 15 didn't conclude, so I would want -- their data in 16 my mind indicates dose-response. How they 17 interpret it -- as I said before, they're two 18 separate things, the production of findings from 19 research and the interpretation of those findings. 20 I am as capable of interpreting -- they 21 aren't as capable of interpreting my findings from 22 my studies as I am or they are as capable -- they 23 have the right to. I have the right to interpret 24 their findings. It's a different activity 25 producing findings and then interpreting them. So</p>

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1 how they interpreted their findings, I don't quite  
 2 remember exactly what they said about it.  
 3 Q Okay.  
 4 MS. BRANSCOME: I am going to pass to  
 5 counsel for Imerys at this time.  
 6 MR. KLATT: Can we go off the record for  
 7 just a couple of minutes? Let me get organized.  
 8 THE VIDEOGRAPHER: We are going off the  
 9 record at 7:31 p.m.  
 10 (Pause in the proceedings.)  
 11 THE VIDEOGRAPHER: We are going back on  
 12 the record at 7:32 p.m.  
 13 DIRECT EXAMINATION  
 14 BY MR. KLATT:  
 15 Q Good afternoon -- good evening,  
 16 Dr. Siemiatycki.  
 17 A Good evening. How are you?  
 18 Q I'm Mike Klatt. I represent Imerys Talc  
 19 America in this case.  
 20 I don't know if you recall or not, but  
 21 you and I had met about two years ago when you  
 22 were giving a deposition in the Oules and Swan  
 23 cases. Do you recall that?  
 24 A I do recall that.  
 25 Q Okay.

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1 A Very fondly.  
 2 Q Thank you.  
 3 I just have a few questions for you, and  
 4 I want to go back and just make sure the record is  
 5 clear on something.  
 6 Your testimony is you've had no contact  
 7 or communications whatsoever with anyone with  
 8 Health Canada regarding talc; is that correct?  
 9 A That's correct.  
 10 Q And you've had no contact or  
 11 communications whatsoever with Dr. Krewski or  
 12 anyone else who's an author of the Taher  
 13 meta-analysis regarding talc?  
 14 A That's correct.  
 15 Q That's correct. Okay.  
 16 A minute ago I believe you told  
 17 Ms. Branscome that if you continued to interact  
 18 with IARC or have contact with Health Canada  
 19 regarding the issue of talc and ovarian cancer,  
 20 it's incumbent upon you to have a conflict of  
 21 interest disclosure, correct?  
 22 A Yes. I said that.  
 23 Q And you would agree with me it would be  
 24 important in evaluating any potential bias you  
 25 have for the people at Health Canada and the

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1 people at IARC and the public generally to know  
 2 that you had been a retained and paid expert by  
 3 plaintiffs' counsel in the talc ovarian cancer  
 4 litigation; is that correct?  
 5 A Sir, can you -- I think I already said  
 6 that, but could you repeat? Maybe I'm  
 7 misunderstanding.  
 8 Q Yes. I'm just saying such a conflict of  
 9 interest disclosure on your part, it would be  
 10 important to disclose not merely that you had been  
 11 a consultant or merely that you had been involved  
 12 in litigation involving ovarian cancer, but it  
 13 would be important to specifically disclose that  
 14 you had been a retained and paid expert by  
 15 plaintiffs' counsel in the talc/ovarian cancer  
 16 litigation. Correct?  
 17 MS. PARFITT: Objection. Form, asked  
 18 and answered.  
 19 THE WITNESS: I -- I'm not sure I  
 20 understand the distinction between this last  
 21 affirmation and the one before. I -- yes, it --  
 22 BY MR. KLATT:  
 23 Q Well, we've had -- we've had other  
 24 conflict of interest disclosures, and I put that  
 25 in quotes, where people said that they had been a

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1 consultant, period. That wouldn't be sufficient,  
 2 would it?  
 3 A I would --  
 4 MS. PARFITT: Objection. Form.  
 5 THE WITNESS: I would not do that.  
 6 BY MR. KLATT:  
 7 Q And we've had people say, I've been  
 8 involved as an expert in ovarian cancer  
 9 litigation. That wouldn't be sufficient either,  
 10 correct?  
 11 MS. PARFITT: Objection. Form.  
 12 THE WITNESS: I would not do that.  
 13 BY MR. KLATT:  
 14 Q What you would do is you would say, I  
 15 have been a retained and paid expert by  
 16 plaintiffs' counsel in the talc/ovarian cancer  
 17 lawsuits, or something essentially equivalent to  
 18 that.  
 19 A I -- I would say something essentially  
 20 equivalent. It's quite possible that if there was  
 21 a submission to a journal, for example, or a  
 22 manuscript, the journal may have a formulaic way  
 23 of expressing that. So...  
 24 Q But wouldn't it be important to the  
 25 readers to know which side of the litigation you

<p style="text-align: right;">Page 278</p> <p>1 had been on in evaluating your bias?</p> <p>2 MS. PARFITT: Objection. Form, asked</p> <p>3 and answered.</p> <p>4 THE WITNESS: I -- I would -- I would</p> <p>5 disclose the nature of my involvement.</p> <p>6 BY MR. KLATT:</p> <p>7 Q Including which side?</p> <p>8 A Including which side I was consulting</p> <p>9 for.</p> <p>10 Q Okay.</p> <p>11 MR. KLATT: Can we mark this as the next</p> <p>12 exhibit?</p> <p>13 MS. PARFITT: 14.</p> <p>14 (Exhibit No. 14 was marked for</p> <p>15 identification.)</p> <p>16 BY MR. KLATT:</p> <p>17 Q Dr. Siemiatycki, you said earlier that</p> <p>18 you worked with Dr. Koushik; is that correct?</p> <p>19 A Yes.</p> <p>20 Q And what is your professional</p> <p>21 relationship with Dr. Koushik?</p> <p>22 A We are members of the same academic</p> <p>23 department. We are down the hall from each other.</p> <p>24 Our offices are nearby each other. We have worked</p> <p>25 together on various projects.</p>	<p style="text-align: right;">Page 280</p> <p>1 PROVAQ study, correct?</p> <p>2 A Correct.</p> <p>3 Q And that's the study she is working on</p> <p>4 with you, correct?</p> <p>5 A More I'm working on with her, but she's</p> <p>6 the lead on that.</p> <p>7 Q And with the help of others in your</p> <p>8 group as well --</p> <p>9 A With the help of others, yes.</p> <p>10 Q -- correct?</p> <p>11 And what I've handed you --</p> <p>12 MR. KLATT: And what was the exhibit</p> <p>13 number?</p> <p>14 MR. TISI: 14.</p> <p>15 BY MR. KLATT:</p> <p>16 Q Exhibit 14 is Dr. Koushik's web pages</p> <p>17 from the Environ Epi website. You're familiar</p> <p>18 with that website, correct?</p> <p>19 A Yes, I am.</p> <p>20 Q And you'll turn to the back page of the</p> <p>21 exhibit, the final page, and you will see it's</p> <p>22 copyrighted 2019, correct?</p> <p>23 A Correct.</p> <p>24 Q And let's just see what Dr. Koushik says</p> <p>25 about her research on the first page. She says:</p>
<p style="text-align: right;">Page 279</p> <p>1 Q For how long?</p> <p>2 A Ten -- 10 or 12 years now.</p> <p>3 Q And she's very well educated, correct?</p> <p>4 MS. PARFITT: Objection.</p> <p>5 THE WITNESS: I'm not sure what you mean</p> <p>6 by that. She has a --</p> <p>7 BY MR. KLATT:</p> <p>8 Q Well, she has a Bachelor --</p> <p>9 A She has a --</p> <p>10 Q -- of Science in pharmacology from the</p> <p>11 University of Alberta.</p> <p>12 A Correct.</p> <p>13 Q She has a Master's in community health</p> <p>14 and epidemiological from Queen's University in</p> <p>15 Kingston, Ontario?</p> <p>16 A Uh-huh.</p> <p>17 Q She has a Ph.D. in epidemiology from --</p> <p>18 in epidemiology and biostatistics from McGill</p> <p>19 University here in Montreal, correct?</p> <p>20 A Correct.</p> <p>21 Q And she's had a postdoctoral fellowship</p> <p>22 at Harvard in the U.S., correct?</p> <p>23 A Correct.</p> <p>24 Q And she is the principal investigator of</p> <p>25 the Prevention of Ovarian Cancer in Quebec, the</p>	<p style="text-align: right;">Page 281</p> <p>1 "My research program focuses on the epidemiology</p> <p>2 of ovarian and lung cancers." Correct?</p> <p>3 A Mm-hmm, yes.</p> <p>4 Q "Ovarian cancer is by far the most</p> <p>5 deadly of all gynecologic cancer. Most patients</p> <p>6 are diagnosed at advanced stages, leading to the</p> <p>7 poor prognosis, and we are currently limited in</p> <p>8 our ability to detect disease early." Correct?</p> <p>9 A Correct.</p> <p>10 Q She says: "There is overwhelming</p> <p>11 evidence that healthy lifestyle choices can reduce</p> <p>12 the risk of several cancers. However, we do not</p> <p>13 yet know of any effective ways to prevent the</p> <p>14 onset of ovarian cancer."</p> <p>15 Would you agree with that?</p> <p>16 MS. PARFITT: Objection. Form.</p> <p>17 THE WITNESS: I'm sorry, I'm trying to</p> <p>18 think of what this sentence really means. It's</p> <p>19 kind of a -- it's kind of a stock sentence that is</p> <p>20 used in -- by epidemiologists when they're looking</p> <p>21 for funding and trying to convince funders that</p> <p>22 we don't know a lot, and therefore they need to</p> <p>23 give us money. So I can imagine part of this is</p> <p>24 cut-and-pasted from that sort of document.</p> <p>25 BY MR. KLATT:</p>

<p style="text-align: right;">Page 282</p> <p>1 Q Well, what it means is --</p> <p>2 MS. PARFITT: Wait, wait. Please let</p> <p>3 him finish.</p> <p>4 BY MR. KLATT:</p> <p>5 Q Go ahead.</p> <p>6 MS. PARFITT: Thanks, Mike.</p> <p>7 THE WITNESS: There are some risk</p> <p>8 factors that are well established for -- for</p> <p>9 ovarian cancer, which Anita is very well aware of,</p> <p>10 genetic and certain reproductive and hormonal</p> <p>11 factors.</p> <p>12 The evidence on talc is accumulating,</p> <p>13 and in my view is sufficient. Anita has not</p> <p>14 reviewed that evidence. And --</p> <p>15 BY MR. KLATT:</p> <p>16 Q Have you talked to Dr. Koushik at all</p> <p>17 about your involvement in the talc ovarian cancer</p> <p>18 litigation?</p> <p>19 A She's aware that I'm involved in this.</p> <p>20 Q Well, let's go on to see what she says</p> <p>21 here.</p> <p>22 After saying: "However, we do not yet</p> <p>23 know of any effective ways to prevent the onset of</p> <p>24 ovarian cancer," she says, "the evidence on some</p> <p>25 lifestyle factors, such as alcohol intake,</p>	<p style="text-align: right;">Page 284</p> <p>1 intake, and recreational physical activity."</p> <p>2 Correct?</p> <p>3 A Correct.</p> <p>4 Q She doesn't say a word about talc there,</p> <p>5 does she?</p> <p>6 MS. PARFITT: Objection. Form.</p> <p>7 THE WITNESS: She doesn't there because</p> <p>8 she hasn't started those analyses yet. She has</p> <p>9 started analyses -- or her -- with students on</p> <p>10 those other factors.</p> <p>11 BY MR. KLATT:</p> <p>12 Q And then flipping over to the next page,</p> <p>13 Dr. Koushik says: "Healthy lifestyle choices may</p> <p>14 also positively impact the health of ovarian</p> <p>15 cancer survivors. Indeed, until we know how to</p> <p>16 prevent ovarian cancers from occurring in the</p> <p>17 first place, cancer control through tertiary</p> <p>18 prevention aimed at improving prognosis and</p> <p>19 quality of life among those diagnosed is</p> <p>20 critical." Correct?</p> <p>21 A Correct.</p> <p>22 Q And again, no mention at all of talc,</p> <p>23 correct?</p> <p>24 MS. PARFITT: Objection. Form.</p> <p>25 THE WITNESS: Correct.</p>
<p style="text-align: right;">Page 283</p> <p>1 physical activity, and smoking, is suggestive but</p> <p>2 currently remains unclear." Correct?</p> <p>3 A Correct.</p> <p>4 Q She doesn't say one word about talc,</p> <p>5 does she?</p> <p>6 A No.</p> <p>7 MS. PARFITT: Objection. Form.</p> <p>8 THE WITNESS: Not here, no.</p> <p>9 BY MR. KLATT:</p> <p>10 Q And then she goes on to say: "More</p> <p>11 research is greatly needed, especially in light of</p> <p>12 recent discoveries that demonstrate that ovarian</p> <p>13 cancer is a heterogeneous disease." She says: "I</p> <p>14 am the principal investigator of the Prevention of</p> <p>15 Ovarian Cancer in Quebec, PROVAQ study, a</p> <p>16 population-based case-control study conducted in</p> <p>17 2011, 2016."</p> <p>18 And one of the things she's evaluating</p> <p>19 in that study is talc, correct?</p> <p>20 A Correct.</p> <p>21 Q "This study provides" -- and I'm reading</p> <p>22 on -- "This study provides a rich data source for</p> <p>23 the study of multiple hypotheses on lifestyle</p> <p>24 factors and ovarian cancer. Current projects</p> <p>25 focus on associations with shift work, caffeine</p>	<p style="text-align: right;">Page 285</p> <p>1 MR. KLATT: Let's mark that.</p> <p>2 MS. PARFITT: This is now 15.</p> <p>3 MR. KLATT: Have we marked that?</p> <p>4 MS. PARFITT: I just now did. I was</p> <p>5 looking for the stickers. I'm going to get one --</p> <p>6 here they are.</p> <p>7 THE WITNESS: I have a different cover.</p> <p>8 MS. PARFITT: It's a different one.</p> <p>9 That's yours.</p> <p>10 THE WITNESS: Oh.</p> <p>11 MS. PARFITT: This is different, this is</p> <p>12 a new item. Let me just put an exhibit on this</p> <p>13 one.</p> <p>14 (Exhibit No. 15 was marked for</p> <p>15 identification.)</p> <p>16 MS. PARFITT: Thank you.</p> <p>17 Okay. You're done with this. And he's</p> <p>18 just showing you this one.</p> <p>19 Do we have an extra copy, Mike, or is</p> <p>20 this it?</p> <p>21 MR. KLATT: I've got an extra copy if</p> <p>22 you need it.</p> <p>23 MS. PARFITT: Okay, that would be great.</p> <p>24 I will give him that one. Thank you very much.</p> <p>25 BY MR. KLATT:</p>

<p style="text-align: right;">Page 286</p> <p>1 Q So, Dr. Siemiatycki, I'm now showing you 2 what we marked as exhibit -- what? 3 MS. PARFITT: 15. 4 MR. KLATT: 15? 5 MS. PARFITT: Yes. 6 BY MR. KLATT: 7 Q And it's from the Environ Epi website, 8 your website, and it's the web pages discussing 9 group research topics, correct? 10 A I -- I have to tell you I don't look at 11 this website, and I haven't actually constituted 12 it. It's my secretary or my assistant who does 13 this. So I'm looking at it afresh to see what's 14 there. Yeah. 15 Q Okay. Let's -- let's turn to the very 16 back page, and again the copyright is 2019. 17 That's this year, correct? 18 A Yeah. Yes. 19 Q And then if you will flip over to -- 20 let's see. Well, let's start -- let's see. 21 Go first page, second page, third 22 page -- the fourth page, there's a discussion 23 there of the PROVAQ study of Dr. Koushik that we 24 just talked about, correct? 25 A Yes.</p>	<p style="text-align: right;">Page 288</p> <p>1 reproductive factors is limited. There is 2 suggestive evidence that modifiable factors in the 3 vitamin D pathway, (sun exposure, diet), and 4 inflammation pathway (antiinflammatory medication 5 use, talc use for feminine hygiene) may play a 6 role in ovarian cancer risk, though this research 7 has been limited by small sample sizes, crude 8 exposure measurement and lack of control for 9 important confounders." Correct? 10 A That's what it says. 11 Q Did I read that correctly? 12 A Yes, you did. 13 Q So on this public website, your 14 Environmental Epi website, Dr. Jack Siemiatycki 15 doesn't say talc use causes ovarian cancer, 16 correct? 17 MS. PARFITT: Objection. Form. 18 THE WITNESS: I don't say anything on 19 that website. 20 BY MR. KLATT: 21 Q Well, you -- your group doesn't say talc 22 causes ovarian cancer, does it? 23 MR. TISI: Objection. Form. 24 THE WITNESS: In my opinion, this was 25 created somewhere around 2009, 2010, 2012, in that</p>
<p style="text-align: right;">Page 287</p> <p>1 Q And the topic says: "Prevention of 2 Ovarian Cancer in Quebec, the PROVAQ study, a 3 case-control study of modifiable and genetic 4 factors associated with the risk of ovarian 5 cancer." Correct? 6 A I see that. 7 Q And it says Anita Koushik, that's 8 Dr. Koushik, who we've just been talking about, 9 and it says Jack Siemiatycki. That's you, 10 correct? 11 A That's right. 12 Q And then it goes on to describe what the 13 PROVAQ study is, and it says -- and I'll skip the 14 first few sentences -- it says: "Primary 15 prevention thus offers the most promising approach 16 to reducing the morbidity and mortality associated 17 with this deadly disease. Established preventive 18 factors for ovarian cancer include high parity, 19 long duration of lactation, oral contraceptive 20 use, and tubal ligation." Correct? 21 A That's what it says. 22 Q Talc is not included in that list of 23 established preventive factors, is it? 24 A It's not listed there, no. 25 Q "However, the ability to modify these</p>	<p style="text-align: right;">Page 289</p> <p>1 ballpark. This feels to me like a cut and paste 2 from the grant application of 2009 or 2010 that 3 hasn't been changed. 4 There's not really a lot of motivation 5 for us to -- besides just sort of putting our 6 names and faces up there, our institution asks us 7 to put something on this institutional website 8 for a researcher. I haven't -- I've never looked 9 at this. 10 BY MR. KLATT: 11 Q You or your organization -- 12 MS. PARFITT: Wait. Mike -- Mike, 13 excuse me, I think we're done. 14 THE WITNESS: I've never contributed to 15 this or looked at it. 16 MS. PARFITT: No, no, Mike, 17 unfortunately, your time is up. 18 MR. KLATT: You've -- 19 MS. PARFITT: Mike, no more questions. 20 I have a few questions. I think we're -- 21 MR. KLATT: Are we -- are we done? 22 THE VIDEOGRAPHER: Yes. 23 MR. KLATT: All right. 24 MS. PARFITT: Thank you. I do have a 25 few.</p>

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1 Dr. Siemiatycki, I'm going to stay right  
2 over here for a moment, okay? And we can get  
3 through this. Okay?  
4 MR. KLATT: Here, I'll give this back to  
5 you.  
6 THE WITNESS: Hi.  
7 MS. PARFITT: Tell me when you are  
8 ready.  
9 THE WITNESS: Who are you?  
10 MS. PARFITT: I know.  
11 MR. TISI: Are we back on? Are we back  
12 on?  
13 THE VIDEOGRAPHER: I didn't stop.  
14 Sorry, I --  
15 MR. TISI: Oh, I thought we were off.  
16 MS. PARFITT: Okay. We didn't -- we  
17 didn't know that.  
18 CROSS-EXAMINATION  
19 BY MS. PARFITT:  
20 Q Dr. Siemiatycki, good evening --  
21 Okay. Dr. Siemiatycki, good evening. I  
22 know it's been a long day, and I have a few  
23 questions, and I will be wrapping -- or jumping  
24 around a bit, so hopefully try and keep pace with  
25 me, and I'll try and speak slowly and -- so that

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1 we can move through the remainder of your  
2 deposition.  
3 Dr. Siemiatycki, do you have an opinion  
4 as to whether the elimination of talcum powder use  
5 in the genital area is a lifestyle activity that  
6 is modifiable?  
7 If you need me to ask the question  
8 again, I'm happy to.  
9 A Yeah, I'm trying to think of how the  
10 word "modifiable" is used.  
11 Q Is it preventable? Is the use of talcum  
12 powder products in the genital area a preventable  
13 activity?  
14 A Yes.  
15 MS. BRANSCOME: Objection.  
16 BY MS. PARFITT:  
17 Q All right. Thank you.  
18 All right. You were asked some  
19 questions about the Taher article. You remember  
20 that?  
21 A Yes.  
22 Q All right. And is it your understanding  
23 that the Taher article is a meta-analysis that was  
24 formed as part of the Health Canada  
25 recommendation?

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1 MS. BRANSCOME: Objection.  
2 THE WITNESS: I think it was ordered --  
3 it was contracted in order to underpin the Health  
4 Canada evaluation. That's my --  
5 BY MS. PARFITT:  
6 Q All right. Now, it was not the only  
7 study or research that was conducted by Health  
8 Canada; is that correct? It was the meta-analysis  
9 that was conducted by them.  
10 MS. BRANSCOME: Objection.  
11 THE WITNESS: Sorry, I -- what --  
12 BY MS. PARFITT:  
13 Q The Taher study --  
14 A Study.  
15 Q -- is a meta-analysis; is that correct?  
16 A Yes. Yes.  
17 Q All right. And the Taher meta-analysis  
18 was one part of the information that formulated  
19 part of the Health Canada draft assessment?  
20 A That's my understanding, yes.  
21 Q All right. Now, Daniel Krewski, you  
22 indicated, was one of the authors of the Taher  
23 paper.  
24 A Yes. He's listed.  
25 Q And I believe you testified that you

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1 know Daniel Krewski.  
2 A Yes, I do.  
3 Q And I believe Mr. Klatt asked you  
4 whether or not you had reached out or perhaps  
5 Ms. Branscome asked you whether or not you have  
6 had any communication with anyone, verbal, oral,  
7 written, that had anything to do with Health  
8 Canada. Do you remember that?  
9 A Yes, I do remember.  
10 Q All right. And it's been many hours,  
11 but it was my understanding in response to that  
12 question, you did indicate that you had sent an  
13 e-mail to Daniel Krewski; is that correct?  
14 MS. BRANSCOME: Objection.  
15 THE WITNESS: I don't remember saying  
16 that.  
17 BY MS. PARFITT:  
18 Q Okay, let me ask you. Have you ever  
19 reached out to any member or author of the Taher  
20 meta-analysis?  
21 A I -- when I learned about it, I sent an  
22 e-mail to Dan Krewski asking if this report was  
23 intended for publication; and if so, when it would  
24 appear, and I haven't -- I didn't have any  
25 response.

<p style="text-align: right;">Page 294</p> <p>1 Q All right. So you have had no 2 communication with any of the authors of the Taher 3 study or any of the members of Health Canada? 4 A No. 5 Q Okay. Now, you were asked some 6 questions with regard to the Schildkraut study in 7 particular. Now, what I'd like you to do is, if 8 you can get that in front of you, and I believe 9 it's part of the documentation in your binder, 10 number 4. 11 And what I'd ask you to also do, if you 12 will, is pull out your paper, your Terry paper -- 13 your copy of the Terry paper, and maybe we'll go 14 there first. 15 A Terry? 16 Q If you get the Terry. Do you have the 17 Terry in front of you? 18 A Yeah, I've got it in front of me, yes. 19 Q Okay. Now, Ms. Branscome asked you and 20 referred you to the abstract of the Terry paper. 21 Do you recall that -- 22 A Yes. 23 Q -- examination? 24 A Yes. 25 Q And I believe she focused your attention</p>	<p style="text-align: right;">Page 296</p> <p>1 you? 2 A Yes, I do. 3 Q And I believe it's a continuation of the 4 Results section -- 5 A Yes. 6 Q -- which starts on 815 and continues all 7 the way over to the end of the document. Do you 8 see that? 9 A I do. 10 Q All right. And specifically about 11 halfway down on page 817 of the Results section of 12 the Terry paper, what did the authors find as it 13 pertains to whether or not there is evidence 14 demonstrating dose-response as it relates to 15 genital powder use and ovarian cancer? 16 A So are you referring to the sentence 17 that begins "Although a significant increase"? 18 Q Correct. 19 A Or before that? 20 Q Whatever you need to read, but I was 21 specifically -- 22 A Okay. 23 Q -- referring to the "although." And you 24 can read that paragraph, please. 25 A Okay. So I'll start at the beginning of</p>
<p style="text-align: right;">Page 295</p> <p>1 on the very last sentence of the Terry paper, the 2 next to last sentence which started with "Among 3 genital powder users." 4 Do you see that? 5 A I see that. 6 Q All right. And she asked you whether or 7 not indeed the abstract section of the Terry paper 8 said: "Among genital powder users, we observed no 9 significant trend, p equals 0.17, in risk with 10 increasing numbers of lifetime applications 11 (assessed in quartiles)." 12 A I see that. 13 Q All right. You've had an opportunity to 14 read this -- 15 A I've read it -- 16 Q -- article? 17 A -- several times over the last three 18 years. 19 Q All right. Let me direct your attention 20 to the actual paper, and specifically to -- not 21 the abstract of the paper but to the section 22 that's entitled -- I believe it's the Discussion 23 section and it's over on page 817. 24 A Yes. 25 Q All right. Do you have that in front of</p>	<p style="text-align: right;">Page 297</p> <p>1 that paragraph. 2 Q Please, if you will. 3 A Read out loud? 4 Q If you will. 5 A "We evaluated cumulative genital powder 6 exposure as a composite variable of frequency and 7 duration of use. We have observed similar 8 increased risks of all nonmucinous subtypes of 9 epithelial ovarian cancer combined across 10 quartiles of genital powder compared with nonuse." 11 The OR in the first quartile is 1.18 with 12 confidence intervals. In the second quartile, it 13 was 1.22. In the third quartile, it's 1.22. And 14 the fourth quartile it's 1.37. 15 I didn't read the confidence intervals. 16 Q Are the confidence intervals for the 17 quartiles you just discussed all statistically 18 significant? 19 A Yes, they are. 20 Q All right. Please continue. 21 A "Although a significant increase in risk 22 with an increasing number of genital powder 23 applications was found for nonmucinous epithelial 24 ovarian cancer when nonusers were included in the 25 analysis with a p-value that's extremely small,"</p>

<p style="text-align: right;">Page 298</p> <p>1 highly significant, "no trend in cumulative use                  2 was evident in analyses restricted to ever users                  3 of genital powder for trend .17. Taken together,                  4 these observations suggest that the significant                  5 trend test largely reflects the comparison of ever                  6 regular use with never use."                  7 Q Okay, and if you would stop there.                  8 What is the significance of the findings                  9 of the authors in that paragraph you just read as                  10 it pertains to whether or not this study shows a                  11 dose-response increase?                  12 A Well, so my interpretation is that                  13 overall there is, for users compared to nonusers,                  14 a highly significant trend, and four -- among the                  15 four - there are four quartiles, and there is a                  16 fifth group called nonusers -- they have a                  17 relative risk of 1.0. And in those five groups,                  18 the relative risk -- the relative risk estimates                  19 go from 1.0 to 1.18 to 1.22, 1.22, 1.3,                  20 something, 7. Those five values indicate to me a                  21 tendency of increasing risk with increasing                  22 exposure. Whether it is -- whether there's formal                  23 proof of that in a -- from a statistical                  24 significance point of view is a secondary issue as                  25 to compared with whether the data are compatible</p>	<p style="text-align: right;">Page 300</p> <p>1 Q The Draft Screening Assessment, right.                  2 A Yes.                  3 Q Okay. And specifically, let me direct                  4 your attention to Roman number -- Roman numeral                  5 III of that document.                  6 A Yes.                  7 Q Okay.                  8 MS. BRANSCOME: Michelle, would you mind                  9 helping me follow along?                  10 MS. PARFITT: Oh, I'm sure.                  11 MR. TISI: I can give you my copy.                  12 MS. PARFITT: Sure. Absolutely.                  13 MR. KLATT: You may want those.                  14 MS. BRANSCOME: Thank you. What page                  15 are we on?                  16 MS. PARFITT: Counsel, I'm on Roman                  17 numeral III.                  18 MS. BRANSCOME: Oh, the page -- I had a                  19 section number that I couldn't find --                  20 MS. PARFITT: No. At the bottom it has                  21 a Roman numeral III.                  22 BY MS. PARFITT:                  23 Q Dr. Siemiatycki, referring you to the --                  24 first, second, third -- fourth full paragraph of                  25 the Draft Screening Assessment, the fourth full --</p>
<p style="text-align: right;">Page 299</p> <p>1 with dose-response.                  2 So as you may recall, in the IARC 2006                  3 evaluation and in -- I guess in the Langseth                  4 paper, I think we indicated that we were very                  5 concerned about the consistency of increased                  6 risks, but found no evidence of dose-response, and                  7 that held back any inference that the                  8 categorization should be greater than a 2B.                  9 The findings from Terry turn on its head                  10 the assumptions that were made at IARC that there                  11 was no evidence of dose-response. Now there is                  12 evidence of dose-response, whether or not it's                  13 significant by one test or another test.                  14 Q All right. Thank you.                  15 All right. Let me direct your                  16 attention, if I may, to the Health Canada                  17 document, specifically the Draft Screening                  18 Assessment dated December 2018. Again, I believe                  19 it's in your notebook 4.                  20 A 6 -- yeah. Yes.                  21 Q All right.                  22 A Okay, I have it.                  23 Q Now -- now --                  24 A Sorry, the Taher or the Draft Screening                  25 Assessment?</p>	<p style="text-align: right;">Page 301</p> <p>1 A Begins with "full"?                  2 Q No, it begins with "The meta-analysis."                  3 A "The meta-analysis." Yep.                  4 Q Correct.                  5 Would you please -- does it state: "The                  6 meta-analysis of the" -- am I reading this                  7 correctly?                  8 "The meta-analysis of the available                  9 human studies in the peer-reviewed literature                  10 indicate a consistent and statistically                  11 significant positive association between perineal                  12 exposure to talc and ovarian cancer."                  13 Did I read that correctly?                  14 A Yes, you did.                  15 Q All right. Is that your opinion,                  16 Dr. Siemiatycki, based upon your review of the                  17 totality of the literature on talc powder --                  18 talcum powder use and ovarian cancer in the                  19 genital area?                  20 A Yes, it is.                  21 Q All right. It goes on to say: "Further                  22 available data are indicative of a causal effect."                  23 Did I read that correctly?                  24 A Yes, you did.                  25 Q All right. Is it your opinion based</p>

<p style="text-align: right;">Page 302</p> <p>1 upon the totality of not only the epidemiological 2 data and findings but mechanistic data, animal and 3 in vivo data, that indeed the data is indicative 4 of a causal effect? 5 MS. BRANSCOME: Objection. 6 MR. KLATT: Objection. Form. 7 THE WITNESS: I believe it is more 8 likely than not that there is a causal 9 relationship between exposure to talc powder and 10 ovarian cancer. And if those two sentences are 11 taken to be equivalent, then I agree with the 12 sentence. 13 BY MS. PARFITT: 14 Q Well, let me ask you this, 15 Dr. Siemiatycki: You've read the draft 16 assessment, and do you have -- is it fair to say 17 that the methodology that the authors performed 18 throughout the course of this particular draft 19 assessment is the same type of methodology that 20 you have performed for purposes of preparing your 21 report and offering the opinions that you have and 22 will continue to offer the court in -- in the 23 litigation involving talcum powder use and ovarian 24 cancer? 25 MS. BRANSCOME: Objection.</p>	<p style="text-align: right;">Page 304</p> <p>1 assessment? 2 MS. BRANSCOME: Objection. 3 THE WITNESS: When you say 4 "methodology" -- 5 BY MS. PARFITT: 6 Q Mm-hmm. 7 A -- I'm not sure if you're referring to 8 sort of high level methodology like collecting 9 original data, evaluating it, weighing it, and 10 making inferences on the basis of that data. 11 BY MS. PARFITT: 12 Q What I'm asking is, did the authors 13 perform a Bradford Hill-like causality assessment 14 in the performance of their study entitled Draft 15 Screening Assessment? 16 MR. KLATT: Objection. Form. 17 THE WITNESS: You're saying in the pages 18 between 15 and -- 19 BY MS. PARFITT: 20 Q Correct. I'll shorten it by -- 21 A -- 21? 22 Q Correct. Correct. 23 And if I can refer your attention to or 24 direct you to page 20. 25 A They commented on various considerations</p>
<p style="text-align: right;">Page 303</p> <p>1 THE WITNESS: The authors of this report 2 I think include a group -- a multidisciplinary 3 group, including toxicologists and possibly 4 environmental scientists. I'm not familiar with 5 them, so I can't say for sure. And in that sense, 6 they cover a broader disciplinary background than 7 I cover myself. So in that sense, they have a 8 broader scope to evaluate the totality of the 9 evidence than I have. 10 Their evaluation of the epidemiologic 11 evidence seems in line with my own, and I have no 12 reason to doubt the validity of their toxicologic 13 analyses of the evidence. 14 BY MS. PARFITT: 15 Q All right. Dr. Siemiatycki, 16 specifically let me refer you to page 15, and it's 17 entitled "Perineal Exposure to Talc." And let me 18 know when you get there. 19 A Yes, I'm there. 20 Q All right. Based upon your review of 21 that section beginning on page 15, and I believe 22 it goes all the way through page 21, are you able 23 to -- do you have a sense as to the methodology 24 again that the authors of the draft assessment 25 employed in order to arrive at their causal</p>	<p style="text-align: right;">Page 305</p> <p>1 that Bradford Hill mentioned in his article. 2 Q And which ones did they provide 3 information and findings on? 4 A They commented on the strength of the 5 association, on consistency, specificity, 6 temporality, biological gradient, biological 7 plausibility, and coherence. 8 Q And what did the authors conclude -- 9 after looking at the various Bradford Hill 10 factors, what did they conclude in that last 11 paragraph of their Bradford Hill assessment? 12 A "Suggests a small but consistent 13 statistically significant positive association 14 between ovarian cancer and perineal exposure to 15 talc. Further available data are indicative of a 16 causal effect." 17 Is it -- is that what you're referring 18 to? 19 Q Yes. And do you agree with the authors 20 of the draft report of December 2018, when they 21 conclude that: "The most recent meta-analysis 22 detailed, Taher 2018, and consistent with the Hill 23 criteria suggest a small but consistent 24 statistically significant positive association 25 between ovarian cancer and perineal exposure to</p>

<p style="text-align: right;">Page 306</p> <p>1 talc. Further available data are indicative of a 2 causal effect"?</p> <p>3 A Yes.</p> <p>4 MR. KLATT: Objection to form.</p> <p>5 BY MS. PARFITT:</p> <p>6 Q Thank you. All right. 7 Let me ask a couple other questions, and 8 I need you -- if you will, can you reach over 9 there, I believe it was exhibit number -- do you 10 see your book on occupational diseases? I think 11 it's under -- there you go. Okay.</p> <p>12 Okay. Now, you were asked many hours 13 ago some questions regarding the book Risk Factors 14 for Cancer in the Workplace.</p> <p>15 Do you recall that?</p> <p>16 A Yes, I do.</p> <p>17 Q All right. And that is indeed a book 18 that was authored by you, Jack Siemiatycki, 19 correct?</p> <p>20 A Correct.</p> <p>21 Q All right. And I believe you were asked 22 whether there was anything in your book that 23 described the methodology that you have employed 24 over the course, and I believe you said the last 25 four decades or almost four decades.</p>	<p style="text-align: right;">Page 308</p> <p>1 you have copies in that binder that you had 2 printed out.</p> <p>3 MS. BRANSCOME: May I have a copy if he 4 is going to read from it?</p> <p>5 MS. PARFITT: Absolutely. And I thought 6 we had -- do you have any copies in there?</p> <p>7 THE WITNESS: Oh, for this --</p> <p>8 MS. PARFITT: No.</p> <p>9 MR. TISI: It wasn't marked. It was in 10 the stuff you printed out.</p> <p>11 MS. PARFITT: I think I've got one here. 12 (A discussion was held off the record.)</p> <p>13 MS. PARFITT: Ms. Branscome, here you 14 go. Here's copies.</p> <p>15 And let's have this marked as now 16 exhibit -- I'm not sure what we're up to.</p> <p>17 MR. TISI: We're up to 18. 18.</p> <p>18 MS. PARFITT: 18. Okay.</p> <p>19 And for the record, we are marking the 20 face sheet of the book Risk Factors for Cancer in 21 the Workplace by Jack Siemiatycki, and 22 specifically the table --</p> <p>23 MS. BRENNAN: I have 16.</p> <p>24 MR. TISI: No, because he marked --</p> <p>25 MS. BRENNAN: Yeah, 14 --</p>
<p style="text-align: right;">Page 307</p> <p>1 Do you recall those questions?</p> <p>2 A Yes, I do.</p> <p>3 MS. BRANSCOME: Objection.</p> <p>4 BY MS. PARFITT:</p> <p>5 Q All right. Where in that book, if there 6 is something in that book, does it describe the 7 methodology that you have employed over the course 8 of the last four decades that you still employ 9 today in your analysis and opinions and findings 10 in the talcum powder product litigation and 11 ovarian cancer?</p> <p>12 MS. BRANSCOME: Object to form.</p> <p>13 THE WITNESS: I'm looking for -- well, I 14 guess the main thing I would -- I would summarize 15 that --</p> <p>16 BY MS. PARFITT:</p> <p>17 Q And could you tell us for the record --</p> <p>18 A Yes.</p> <p>19 Q -- Dr. Siemiatycki, where you are?</p> <p>20 A Where I'm reading?</p> <p>21 Q Yes, please.</p> <p>22 A Thank you. I'm looking at page 298 in 23 this book, and I -- did you provide a copy of that 24 chapter?</p> <p>25 MR. TISI: Doctor, you have copies --</p>	<p style="text-align: right;">Page 309</p> <p>1 MR. KLATT: Actually, it should be 16.</p> <p>2 MS. PARFITT: 16? Thank you. 16.</p> <p>3 All right. We are now marking as 4 Exhibit 16 the book entitled Risk Factors for 5 Cancer in the Workplace by Dr. Jack Siemiatycki, 6 which specifically includes the table of contents, 7 Chapter 7, "Interpretation of Findings," pages 297 8 through 308.</p> <p>9 MR. DONATH: Is that an excerpt, not the 10 whole thing?</p> <p>11 MS. PARFITT: It is -- it is not. We'll 12 make the book available, but it's just the 13 excerpt.</p> <p>14 (Exhibit No. 16 was marked for 15 identification.)</p> <p>16 MS. BRANSCOME: Did someone just join 17 the line?</p> <p>18 THE REPORTER: They hung up.</p> <p>19 THE WITNESS: Shall I read a couple of 20 paragraphs from this?</p> <p>21 BY MS. PARFITT:</p> <p>22 Q Well, the question was -- the question 23 was whether or not there was any bases or writings 24 that discussed the methodology that you've 25 employed over the last four decades, and you</p>

<p style="text-align: right;">Page 310</p> <p>1 commented that it was in your book.  2 MS. BRANSCOME: Object --  3 BY MS. PARFITT:  4 Q So please tell us what's in your book.  5 MS. BRANSCOME: Object to form.  6 THE WITNESS: Well, I -- I won't read  7 the whole book.  8 BY MS. PARFITT:  9 Q I appreciate that. We all --  10 A I have a phone book downstairs that I  11 could -- no, I will just read a couple of  12 paragraphs that talk about interpreting and  13 conducting epidemiologic research in general, not  14 specifically related to this particular study --  15 set of studies that I describe in the book.  16 "The main purpose of epidemiology is to  17 find the cause of disease. Despite some  18 controversy concerning the validity of drawing  19 causal inferences in epidemiology. There is a  20 consensus that sanctions and provides guidelines  21 for the practice. The evaluation of causality  22 between a putative risk factor and disease is a  23 complex and subjective process. Equally competent  24 scientists examining the same information can  25 arrive at different conclusions. However, as</p>	<p style="text-align: right;">Page 312</p> <p>1 Is that what you were --  2 Q That's what I wanted to know.  3 A -- asking?  4 Q Thank you. All right.  5 Now, do you recall, Dr. Siemiatycki,  6 that you were asked some questions about the  7 mechanism underlying exposure to talc and genital  8 use of talcum powder products and ovarian cancer?  9 Do you remember Ms. Branscome asked you some  10 questions about that?  11 A The mechanism of exposure or the  12 mechanism of carcinogenesis?  13 Q The mechanism of exposure --  14 A Okay.  15 Q -- between talcum powder products and  16 ovarian cancer. Do you remember there were a  17 series of questions that were asked about that?  18 MS. BRANSCOME: Object to form.  19 THE WITNESS: I'm -- I'm not --  20 BY MS. PARFITT:  21 Q Okay. Let me -- okay. Let me -- let me  22 do this. Let me refer you to your report, if you  23 will, and I believe it's been marked as -- I think  24 this is 10 -- as 10.  25 Do you have your report in front of you?</p>
<p style="text-align: right;">Page 311</p> <p>1 additional evidence is accumulated, beliefs and  2 consensuses may change. The criteria that are  3 most relevant to the problem of evaluating  4 causality between cancer and an antecedent  5 occupational exposure may be paraphrased as  6 follows:  7 Number 1: "Is sampling variability a  8 plausible explanation for the observed  9 association?"  10 Number 2: "How strong is the  11 association and is there a dose-response  12 relationship?"  13 Number 3: "Is bias or confounding a  14 plausible explanation for the observed  15 association?"  16 Number 4: "Is the association  17 biologically plausible?"  18 Number 5: "Is there relevant supporting  19 evidence from other epidemiologic studies or from  20 non-human test systems, such as animal  21 experimentation or tests of mutagenicity?"  22 I'll stop there. But in answer to your  23 question, this text, published 30 years ago now,  24 encapsulates my approach to how to interpret and  25 use epidemiologic evidence in assessing causality.</p>	<p style="text-align: right;">Page 313</p> <p>1 A Yes.  2 Q Very good. Okay.  3 All right. And specifically I'm  4 referring to page 64 and 65.  5 A So I'm one or two pages off, so just  6 tell me which section.  7 Q Okay. I believe it's -- it's under  8 "Biological Plausibility." Do you see that in the  9 lower part? Let's see.  10 A "Biological Plausibility" -- (reading to  11 himself.) Strength. Okay. I've got it  12 somewhere -- consistency. Here.  13 Q Okay.  14 A "Biological Plausibility," yes.  15 Q Now, I specific -- I believe  16 specifically the question that you were asked is  17 whether or not you will be testifying with regard  18 to the mechanism and the biological mechanism for  19 causing cancer with genital use of talcum powder  20 products. Do you remember that?  21 A Yes.  22 Q Okay. Now, in the course of your  23 analysis and in looking at that issue of  24 biological mechanism for causing cancer, what did  25 you consult and review and assess for purposes of</p>

<p style="text-align: right;">Page 314</p> <p>1 formulating your opinions on that topic?  2 MS. BRANSCOME: Objection.  3 THE WITNESS: I actually started with  4 the IARC 2006 report where there was a high level  5 subgroup of toxicologists and basic scientists who  6 reviewed the evidence. So I read that material.  7 I've read various articles concerning  8 migration of particles, articles about  9 inflammation as a carcinogenic process, oxidative  10 stress as part of the carcinogenic process. And  11 towards the end, started looking at articles about  12 asbestos in talc as filling in some of the  13 information about what the content of talcum  14 powder products were. I at one point was looking  15 at company documents to try to figure out what  16 were the time relationships of using talc versus  17 using substitutes for talc. So all of those kinds  18 of things I was looking for.  19 BY MS. PARFITT:  20 Q So for purposes of evaluating the  21 evidence and opining on the issue of talcum powder  22 products and ovarian cancer, did you consider the  23 issue of biological plausibility?  24 MS. BRANSCOME: Objection.  25 THE WITNESS: Yes, I considered it.</p>	<p style="text-align: right;">Page 316</p> <p>1 causality.  2 So the bar for establishing plausibility  3 for me is, are there credible scientists who are  4 persuaded or have reasonable confidence that there  5 is a mechanism that can explain the observation.  6 And if so, I would defer to that point of view as  7 being plausible.  8 I would not accept that one or more  9 scientists developing a mechanistic theory are  10 definitely proven, but if there is a credible  11 point of view in the scientific community about  12 the mechanism, I would call that plausible. It  13 doesn't mean it's proven. It's plausible.  14 And to my satisfaction, when I looked at  15 the different reports, including reports of  16 experts in the litigations, I was reasonably  17 assured that there are plausible theories and  18 plausible hypotheses.  19 Q All right. In your section of your  20 expert report on page 64 through 66, did the  21 factors you identify under the subtitle  22 "Biological Plausibility" provide support for your  23 opinions that indeed there is biological  24 plausibility between the use of genital use of  25 talcum powder products and ovarian cancer?</p>
<p style="text-align: right;">Page 315</p> <p>1 BY MS. PARFITT:  2 Q All right. And what was the basis of  3 your opinion as to whether or not there was  4 biological plausibility between talcum powder  5 product use in the genital area and ovarian  6 cancer?  7 MS. BRANSCOME: Objection. Assumes he  8 formed an opinion.  9 THE WITNESS: Well, my --  10 BY MS. PARFITT:  11 Q Dr. Siemiatycki, did you formulate an  12 opinion with regard to whether there was  13 biological plausibility between the use of talcum  14 powder products and ovarian cancer?  15 A Yes, I did.  16 Q Okay.  17 A And the first part of the discussion is  18 what one means by "plausibility." And so one  19 issue that I took off the table quite soon is the  20 notion that biological plausibility is synonymous  21 with biological proof. Neither Bradford Hill nor  22 anyone else who has described the use of  23 biological plausibility as a criterion has ever  24 claimed that biological proof of a mechanism is  25 necessary before you can opine about the -- about</p>	<p style="text-align: right;">Page 317</p> <p>1 A I think they provide evidence of  2 plausibility for those theories.  3 Q And did you consider those for purposes  4 of opining that talcum powder products in the  5 genital area, used, can cause ovarian cancer?  6 A Yes, I considered them.  7 Q All right. Dr. Siemiatycki, I'm not  8 sure of the -- I don't think we marked it as an  9 exhibit, so let me do that now. I believe we're  10 up to 17.  11 (A discussion was held off the record.)  12 (Exhibit No. 17 was marked for  13 identification.)  14 BY MS. PARFITT:  15 Q All right. Dr. Siemiatycki, do you  16 recall the discussion you had with Ms. Branscome,  17 again several hours ago, on the issue of  18 confounding and how that can impact study designs?  19 A Oh, yes.  20 Q All right. Let me show you a document  21 we have marked as Exhibit No. 17, and it's  22 entitled "Degree of confounding bias related to  23 smoking ethnic group, and socioeconomic status and  24 estimates of the association between occupation  25 and cancer," and I believe that's an article that</p>

<p style="text-align: right;">Page 318</p> <p>1 you were an author, correct?</p> <p>2 A That's correct, yes.</p> <p>3 Q All right. What, if any, support did</p> <p>4 that particular article that you wrote, I guess</p> <p>5 back in 1988, provide, if any, for the opinions</p> <p>6 that you've rendered in this case on the topic of</p> <p>7 confounding and bias?</p> <p>8 A In this study we evaluated 75</p> <p>9 associations, 25 occupations in relation to lung</p> <p>10 cancer, to bladder cancer and to stomach cancer,</p> <p>11 each of them. And we looked at the association</p> <p>12 between each occupation and each of the three</p> <p>13 types of cancer, adjusting for the smoking history</p> <p>14 of the patients and the subjects. But another set</p> <p>15 of analyses not adjusting for their smoking</p> <p>16 histories, and their socioeconomic status and</p> <p>17 their ethnic group. These are factors that are</p> <p>18 strongly associated with cancer and with different</p> <p>19 occupations. We wanted to see how large a</p> <p>20 confounding bias could be generated by not having</p> <p>21 proper confounder information.</p> <p>22 And so I will just read a couple of</p> <p>23 sentences from the abstract of this article.</p> <p>24 "Of the 75 associations studied, only</p> <p>25 one OR was distorted by more than 40 percent. A</p>	<p style="text-align: right;">Page 320</p> <p>1 low probability.</p> <p>2 And this is part of what leads me and</p> <p>3 what led me in my report to opine that confounding</p> <p>4 is unlikely to be the explanation for the observed</p> <p>5 relative risks.</p> <p>6 Q Thank you. All right.</p> <p>7 THE VIDEOGRAPHER: Excuse me, Counsel.</p> <p>8 MS. PARFITT: Off the record, yes.</p> <p>9 THE VIDEOGRAPHER: Off the record?</p> <p>10 MS. PARFITT: Yeah, it's a good time,</p> <p>11 because you're running out of tape. I could tell.</p> <p>12 THE VIDEOGRAPHER: Going off the record</p> <p>13 at 8:27 p.m.</p> <p>14 (Recess.)</p> <p>15 THE VIDEOGRAPHER: We're going back on</p> <p>16 the record at 8:31 p.m.</p> <p>17 MS. PARFITT: Thank you.</p> <p>18 BY MS. PARFITT:</p> <p>19 Q Dr. Siemiatycki, just one last question.</p> <p>20 Let me direct your attention to again</p> <p>21 the documents in your Exhibit No. 4, specifically</p> <p>22 the "Weight of Evidence: General Principles and</p> <p>23 Current Applications at Health Canada," which</p> <p>24 formed part of the Health Canada recommendation.</p> <p>25 All right?</p>
<p style="text-align: right;">Page 319</p> <p>1 40 percent distortion would correspond to an odds</p> <p>2 ratio of 1.4 when comparing unadjusted with</p> <p>3 adjusted estimates. Three were distorted by</p> <p>4 between 30 percent and 40 percent, and four others</p> <p>5 by between 20 percent and 30 percent."</p> <p>6 So of these 75 associations, not taking</p> <p>7 account of very powerful confounders -- smoking is</p> <p>8 the most powerful confounder we know. Ethnicity</p> <p>9 and socioeconomic status are important</p> <p>10 confounders. They have strong relative risks with</p> <p>11 these different cancers. Not taking them into</p> <p>12 account could create artifactual odds ratios,</p> <p>13 maximum of 1.4, even though the original odds</p> <p>14 ratios of the confounders with these cancers could</p> <p>15 be as high as 10.</p> <p>16 So there's a very -- the confounding</p> <p>17 effect, at most, would be 10 percent or 20</p> <p>18 percent, but the likelihood that there is some</p> <p>19 unknown confounder with -- with ovarian cancer</p> <p>20 that is artifactually creating across the board,</p> <p>21 across all these studies, an artifactual relative</p> <p>22 risk of around 1.3 would require some -- that</p> <p>23 unknown confounder to have an extremely high</p> <p>24 relative risk, certainly higher than 2, maybe</p> <p>25 higher than 3 or 4, which is not inconceivable but</p>	<p style="text-align: right;">Page 321</p> <p>1 A I'm not sure if it formed part of the</p> <p>2 recommendation or if it's a background document.</p> <p>3 Q Very good. I think you're probably</p> <p>4 right.</p> <p>5 All right. And you have -- you have had</p> <p>6 a chance to review that, correct?</p> <p>7 A Yes.</p> <p>8 Q All right. Specifically let me direct</p> <p>9 your attention to page 7 of that document. And</p> <p>10 I'm going to go down to the very last paragraph,</p> <p>11 and it starts with: "The majority of risk</p> <p>12 assessment reports, however, provide a logical</p> <p>13 narrative description of the relative strengths or</p> <p>14 weakness of various lines of evidence considered.</p> <p>15 For most risk assessments, individual lines of</p> <p>16 evidence are polled and integrated into a final</p> <p>17 conclusion based on best professional judgment and</p> <p>18 not mathematical formula."</p> <p>19 Did I read that correctly?</p> <p>20 A Yes, you did.</p> <p>21 Q Do you agree with the statement by</p> <p>22 Health Canada in their "Weight of Evidence:</p> <p>23 General Principles"?</p> <p>24 A Yes, I do.</p> <p>25 MS. PARFITT: All right. I have no</p>

<p style="text-align: right;">Page 322</p> <p>1 further questions. Thank you.</p> <p>2 THE WITNESS: This is also in conformity</p> <p>3 with all guidelines from agencies and experts who</p> <p>4 understand science.</p> <p>5 MS. PARFITT: Very good.</p> <p>6 THE WITNESS: The best data is</p> <p>7 collected, compiled, and then interpreted by human</p> <p>8 expert judgment.</p> <p>9 MS. PARFITT: Thank you very much,</p> <p>10 Dr. Siemiatycki. I believe counsel has some</p> <p>11 follow-up.</p> <p>12 MS. BRANSCOME: I do, but I think I need</p> <p>13 to take a break to confer amongst ourselves.</p> <p>14 MS. PARFITT: Go ahead.</p> <p>15 THE VIDEOGRAPHER: We're going off the</p> <p>16 record at 8:33 p.m.</p> <p>17 (Recess.)</p> <p>18 THE VIDEOGRAPHER: We are going back on</p> <p>19 the record at 8:46 p.m.</p> <p>20 REDIRECT EXAMINATION</p> <p>21 BY MS. BRANSCOME:</p> <p>22 Q Good evening, Dr. Siemiatycki.</p> <p>23 I have some follow-up questions to the</p> <p>24 questions that were just asked to you by</p> <p>25 plaintiffs' counsel.</p>	<p style="text-align: right;">Page 324</p> <p>1 gist of it was whether the paper has been or will</p> <p>2 be submitted for publication. I don't recall if</p> <p>3 there were other important components. It was a</p> <p>4 brief message, besides pleasantries of people</p> <p>5 who've known each other for 30 years.</p> <p>6 But, you know, I said I -- I've learned</p> <p>7 about this work that you were involved with. I</p> <p>8 can't remember what else I said.</p> <p>9 Q In your e-mail communication to</p> <p>10 Dr. Krewski, did you alert him to the fact that</p> <p>11 you were serving as a -- an expert on behalf of</p> <p>12 plaintiffs' counsel in litigation involving talcum</p> <p>13 powder?</p> <p>14 A I don't recall. Your question used the</p> <p>15 plural, and in my -- you said "in your</p> <p>16 communications." That's what I heard. No? Okay.</p> <p>17 Q I meant it in the singular.</p> <p>18 A You meant it in the singular, so I guess</p> <p>19 the record will reflect.</p> <p>20 In my one message to Dr. Krewski -- let</p> <p>21 me -- if I may.</p> <p>22 Q My question again, Dr. Siemiatycki --</p> <p>23 A Yeah, please.</p> <p>24 Q -- is in your e-mail to Dr. Krewski with</p> <p>25 respect to the Taher paper, did you notify him in</p>
<p style="text-align: right;">Page 323</p> <p>1 Both myself and counsel for Imerys asked</p> <p>2 you very specifically if you had had contact with</p> <p>3 any of the authors in connection with the Taher</p> <p>4 paper or the Health Canada paper. Do you recall</p> <p>5 the questions that we asked you?</p> <p>6 A I -- I recall that you asked questions</p> <p>7 about it, yes.</p> <p>8 Q Yeah. Is there a reason why during my</p> <p>9 questioning and questioning by counsel for Imerys</p> <p>10 you did not recall having sent an e-mail to</p> <p>11 Dr. Krewski with respect to the potential</p> <p>12 publication of the Taher paper?</p> <p>13 A I -- I guess I consider -- well, two</p> <p>14 parts. I consider a contact sort of a two-way</p> <p>15 process, and there was no two-way process. I sent</p> <p>16 him a message. He never responded.</p> <p>17 And number two, it -- it dropped off of</p> <p>18 my memory screen. I -- I just forgot about it</p> <p>19 until she asked.</p> <p>20 Q When did you contact Dr. Krewski about</p> <p>21 the Taher paper?</p> <p>22 A In December, when I first learned about</p> <p>23 it.</p> <p>24 Q What specifically did you ask him?</p> <p>25 A My recollection, I asked him if -- the</p>	<p style="text-align: right;">Page 325</p> <p>1 that e-mail that you were serving as an expert</p> <p>2 witness retained on behalf of plaintiffs' counsel</p> <p>3 in litigation involving talcum powder?</p> <p>4 A I -- I -- I don't recall if I did or</p> <p>5 not. I -- I wouldn't have thought it was a</p> <p>6 crucial thing to indicate in this first message</p> <p>7 asking him if his paper was in press or in</p> <p>8 publication or something like that.</p> <p>9 Q Why did you want to know whether it had</p> <p>10 been submitted for publication?</p> <p>11 A I wanted to know what the status of that</p> <p>12 report was. I had no -- I didn't follow up my --</p> <p>13 it wasn't an important issue for me. I was -- it</p> <p>14 was kind of an idle gesture of, you know, Hi, I</p> <p>15 haven't heard from you for a while. I see that</p> <p>16 you have this thing. Are you sending it for</p> <p>17 publication? Something like that.</p> <p>18 And I -- the motivation, was there a</p> <p>19 specific ulterior motive? No, there was no --</p> <p>20 there was nothing I would have done differently.</p> <p>21 I guess if he had told me, yes, it's about to be</p> <p>22 submitted, I would have wanted to see the final</p> <p>23 version, because the version that I saw was</p> <p>24 obviously an early manuscript. It was much too</p> <p>25 long for a -- for a publication submission. But</p>

<p style="text-align: right;">Page 326</p> <p>1 it wasn't a big deal for me to -- to have 2 information about that manuscript. 3 Q Including communications in which you 4 unilaterally reached out to individuals but may 5 not have received a response, have you 6 communicated in any form with any of the 7 participants in the development of the Health 8 Canada Draft Screening Assessment or the Taher 9 paper, other than what we have discussed with 10 respect to Dr. Krewski? 11 A No. 12 Q The Health Canada Draft Screening 13 Assessment, you were asked a number of questions 14 about that by counsel for plaintiffs. Is that a 15 document that you have reviewed closely in forming 16 your opinions in this case? 17 MS. PARFITT: Objection. Form. 18 THE WITNESS: I wouldn't say that I 19 reviewed it closely the way I've reviewed the 20 evidence before submitting my report. No. 21 BY MS. BRANSCOME: 22 Q All right. I want to talk to you about 23 Exhibit 17. You have that over there. It's the 24 "Degree of confounding bias related to smoking." 25 A Oh, yeah.</p>	<p style="text-align: right;">Page 328</p> <p>1 Did I read that correctly? 2 MS. PARFITT: Counsel, just with one 3 correction. It came out as "estimates." The 4 article says "estimates," and it came out on the 5 transcript as "assessments." 6 MS. BRANSCOME: Okay. 7 THE WITNESS: That -- do you understand 8 what she's indicated? 9 BY MS. BRANSCOME: 10 Q Yes. Did I read it correctly? 11 A You misread one word. 12 Q Okay. 13 A But it's not important, but if you want 14 to have it for the record. 15 Q Well, we can continue on. 16 A Yes. 17 Q "This consideration follows from the 18 recognition that some degree of bias is quite 19 likely in any non-experimental study." 20 Did I read that correctly? 21 A Yes. 22 Q "Small excess relative risks, even if 23 they are statistically significant, are often 24 interpreted with great caution, if not 25 skepticism."</p>
<p style="text-align: right;">Page 327</p> <p>1 Q All right. Dr. Siemiatycki, is 2 Exhibit 17 an article that you identified to 3 address the likelihood that a confounding variable 4 could explain the increased risk that you have 5 found in your meta-analysis with respect to the 6 use of talc? 7 A Yes. 8 Q Okay. So I just want to direct you to 9 page 623. In the right-hand column, do you see a 10 paragraph that begins "One of the criteria"? 11 A Yes. 12 Q Does it state: "One of the criteria 13 used by epidemiologists to distinguish true from 14 false associations is the strength of the 15 association"? Did I read that correctly? 16 A Yes, you did. 17 Q And again, this is an article on which 18 you are the lead author, correct? 19 A Correct. 20 Q It continues on: "That is, among two 21 relative risk assessments which have equal levels 22 of statistical significance but one of which is 23 much greater than 1, while the other is closer 24 to 1, the larger one is considered more likely to 25 reflect a true association than the smaller one."</p>	<p style="text-align: right;">Page 329</p> <p>1 Did I read that correctly? 2 A Yes. 3 Q "Although there has been no explicit 4 consensus on what level of excess relative risk 5 should be considered too small to be taken 6 seriously, we believe that many epidemiologists 7 use a cut point in the range of 1.2 to 1.5 for 8 this purpose. Our results indicate that a cut 9 point in this range is reasonable for studies of 10 cancer occupation associations." 11 Did I read that correctly? 12 A Yes, you did. 13 Q And the references in those sentences to 14 the words "we" and "our" would include you, 15 Dr. Siemiatycki, correct? 16 A Correct. 17 Q And then if we could turn the page to 18 page 624, the paragraph at the top on the 19 left-hand column, I direct your attention to the 20 last complete sentence of that paragraph. 21 "On the other hand, our results also 22 imply that relative risk estimates as low as 1.2 23 for lung cancer associations or 1.1 for bladder or 24 stomach cancer associations run a fair chance of 25 being attributable to confounding bias, even if</p>

<p style="text-align: right;">Page 330</p> <p>1 they are," quote, "statistically significant."  2 Did I read that correctly?  3 A Yes, you did.  4 Q Is that a conclusion that you and your  5 authors reached in the paper that's been  6 identified as Exhibit 17?  7 A Yes, it was.  8 Q Your opinion with respect to the  9 existence of biological plausibility of the  10 perineal use of talc and ovarian cancer is limited  11 to the evaluation of whether or not there are  12 credible scientists who are persuaded that there  13 is a mechanism; is that correct?  14 MS. PARFITT: Objection. Form.  15 THE WITNESS: Can you repeat that? I'm  16 sorry.  17 BY MS. BRANSCOME:  18 Q Your opinion with respect to the  19 existence of biological plausibility of the  20 perineal use of talc and its potential to cause  21 ovarian cancer is limited to an evaluation of  22 whether or not there are credible scientists who  23 are persuaded that there is a mechanism, correct?  24 MS. PARFITT: Objection. Form.  25 Misstates his testimony.</p>	<p style="text-align: right;">Page 332</p> <p>1 MS. PARFITT: Object to form.  2 THE WITNESS: Correct.  3 BY MS. BRANSCOME:  4 Q You indicated in response to questions  5 by plaintiffs' counsel that you were persuaded by  6 the opinions of other experts in the litigation  7 with respect to biological plausibility. Who are  8 those experts?  9 A I -- I think I indicated that such  10 experts contributed to the information that I had,  11 not that they were the only ones who persuaded me.  12 So there was literature and there were depositions  13 and reports.  14 So -- I'm trying to remember the names  15 of the various expert reports that I have read and  16 depositions. I do -- there's the Plunkett, the  17 Saed papers, but I don't know if there was a  18 report by Saed. There was -- let me look in my  19 list of references. (Peruses document.)  20 I'm sorry, I'm drawing a blank on the  21 names of the people whose reports and testimonies  22 I've read in the last month or two.  23 Q When were you provided with copies of  24 these expert reports?  25 A In the fall. Some before November 15th</p>
<p style="text-align: right;">Page 331</p> <p>1 THE WITNESS: I would say is based on,  2 rather than is limited to.  3 BY MS. BRANSCOME:  4 Q Do you have expertise that would allow  5 you to determine what the most likely biological  6 mechanism is, if there is one, for perineal use of  7 talc to cause ovarian cancer?  8 A No, I wouldn't pretend to -- to have  9 that kind of expertise.  10 Q Okay. Is it also true that you are not  11 qualified to opine on the ability or not of talc  12 particles to migrate to the ovaries from the use,  13 the perineal application of talc?  14 MS. PARFITT: Objection. Form.  15 THE WITNESS: Not on the basis of my  16 research, not on the basis of my training, but on  17 the basis of my reading of literature concerning  18 that issue, I have an opinion based on what I've  19 read from experts in the -- that field.  20 BY MS. BRANSCOME:  21 Q But in forming that opinion, you are  22 relying on --  23 A Yes.  24 Q -- the expertise of others, correct?  25 A Yes.</p>	<p style="text-align: right;">Page 333</p> <p>1 and some after November 15th. And -- but also  2 I'm -- I'm reflecting on the various reports and  3 testimonies from the earlier trial, and I read  4 various expert reports from that time.  5 Q Did you draft the section in your MDL  6 expert report related to biologic plausibility?  7 A Yes, I did.  8 Q You personally summarized each of the  9 various studies that you refer to in that section?  10 A What do you mean by summarized the  11 studies? I -- I summarized the evidence that's  12 captured there, and I provided references for  13 those statements, yes.  14 Q You're the original author of the  15 language in that section is my question.  16 A Yes. Yes.  17 Q Can you identify for me which expert  18 reports related to biological plausibility you had  19 reviewed before forming your opinion as  20 represented in the MDL report?  21 A As I said, it's partly a number of  22 reports that I had seen in the previous trial, and  23 I -- I'm drawing a blank on the names of -- of the  24 people.  25 Q You understand that there will be</p>

<p style="text-align: right;">Page 334</p> <p>1 experts retained by defense counsel who will 2 provide reports addressing biological 3 plausibility, correct? 4 A I assume so, yeah. 5 Q Okay. Are you qualified to evaluate 6 between competing expert reports who is correct 7 about the biological mechanism? 8 MS. PARFITT: Objection. Form. 9 BY MS. BRANSCOME: 10 Q To the extent one exists. 11 MS. PARFITT: Objection. Form. 12 THE WITNESS: No -- no, I wouldn't be. 13 I mean I -- I can read reports from people outside 14 my area and form an opinion about the general 15 coherence and -- and form an initial sense of the 16 credibility of the various reports. And I'd be 17 happy to review the reports of the experts for the 18 defense on these issues. 19 BY MS. BRANSCOME: 20 Q But to the extent, for example, that 21 there are credible experts on both sides of the 22 debate, whether or not there has been an 23 established biological mechanism and whether or 24 not there have not been, you are not qualified to 25 evaluate between the two credible experts?</p>	<p style="text-align: right;">Page 336</p> <p>1 THE VIDEOGRAPHER: We are going off the 2 record at 9:05 p.m. 3 (Pause in the proceedings.) 4 THE VIDEOGRAPHER: We're back on the 5 record at 9:06 p.m. 6 MS. BRANSCOME: At this time I will pass 7 questioning to counsel for Imerys. 8 MS. PARFITT: Thank you. 9 REDIRECT EXAMINATION 10 BY MR. KLATT: 11 Q Dr. Siemiatycki, a few more questions, 12 sir. 13 I'm going to read a statement and ask if 14 you agree with it. Okay? 15 A Yes. 16 Q "When a pronounced binary association is 17 present, use of the never or no category in 18 assessing trend can induce a trend where none 19 exists." 20 A Okay. Can you -- yeah, thank you. 21 Q And my question is, do you agree or 22 disagree with that statement? 23 A Yes, I agree it can -- I agree with it. 24 There are some qualifiers that I would add to that 25 sentence, but I agree with it.</p>
<p style="text-align: right;">Page 335</p> <p>1 MS. PARFITT: Objection. Form. 2 THE WITNESS: That's correct. And I've 3 never pretended that -- make -- that it is 4 necessary for me to establish the correct 5 biological mechanism before drawing inferences 6 about causality. 7 BY MS. BRANSCOME: 8 Q It is your conclusion that more likely 9 than not perineal use of talc can cause ovarian 10 cancer is based on the epidemiological evidence, 11 correct? 12 MS. PARFITT: Objection. Misstates his 13 evidence and testimony today. 14 THE WITNESS: In part -- in large part. 15 Yes. 16 BY MS. BRANSCOME: 17 Q Okay. Well, my question now is about 18 the, in small part, the evidence in addition to 19 that. What evidence are you considering that you 20 are qualified to independently evaluate? 21 A I am qualified to evaluate whether there 22 is a plausible theory about it. Not to establish 23 whether that theory is correct or not. 24 MS. BRANSCOME: Okay. All right. If we 25 could just go off the record very briefly.</p>	<p style="text-align: right;">Page 337</p> <p>1 Q Could you look at your report, please, 2 sir, in the case on page 65, the discussion of 3 biologic plausibility. 4 A Yes. 5 Q And actually I think your biologic 6 plausibility discussion actually begins near the 7 bottom of the previous page, 64, and there's a 8 general discussion on the rest of 64 and the first 9 paragraph or two of 65. Is that correct? 10 A I -- I believe it's correct. The 11 version I have in front of me is that version that 12 has a slightly different formatting, so -- but I'm 13 with you. 14 Q Okay. 15 MS. PARFITT: And I believe, just for 16 completeness, it starts on 60 -- 17 THE WITNESS: Mine starts on -- 18 MS. PARFITT: His document starts on 65, 19 goes all the way over to 66. Mike, yours probably 20 starts on the bottom of 64, goes all the way over 21 to the top of 66. 22 BY MR. KLATT: 23 Q And what I'm focusing on is the 24 paragraph that you wrote that begins with 25 "Insofar" --</p>

<p style="text-align: right;">Page 338</p> <p>1 A Yes.</p> <p>2 Q -- which is where your specific</p> <p>3 discussion of biologic plausibility regarding</p> <p>4 talcum powder products begins.</p> <p>5 A Yes.</p> <p>6 Q Do you -- do you see that paragraph,</p> <p>7 sir?</p> <p>8 A Yes, I do.</p> <p>9 Q And moving down, did you read the</p> <p>10 articles that you cited here carefully?</p> <p>11 A I read them. I'm not capable of fully</p> <p>12 understanding articles in areas that are outside</p> <p>13 my area of -- of expertise. But to the --</p> <p>14 Q Well --</p> <p>15 MS. PARFITT: Wait, let him finish.</p> <p>16 THE WITNESS: To the extent that I was</p> <p>17 able to understand them, I read these articles.</p> <p>18 BY MR. KLATT:</p> <p>19 Q I'm focusing on the sentence that you</p> <p>20 wrote in your report saying: "First of all, there</p> <p>21 are two possible routes that talcum powder</p> <p>22 products can take to reach the ovaries."</p> <p>23 Do you see where I am?</p> <p>24 A Yes, I do.</p> <p>25 Q The next sentence says: "There is</p>	<p style="text-align: right;">Page 340</p> <p>1 A I think so. Is this --</p> <p>2 Q And the --</p> <p>3 A Is this the South African study?</p> <p>4 Q I believe you're right.</p> <p>5 A Okay.</p> <p>6 Q And the women were not women using</p> <p>7 perineal talc. They were women who were being</p> <p>8 prepared to undergo gynecologic surgery, correct?</p> <p>9 A Correct.</p> <p>10 Q And after this solution of albumin</p> <p>11 microspheres was injected at the top of the</p> <p>12 vaginal vault, the women were tilted in a head</p> <p>13 down/pelvis up position for two hours beforehand,</p> <p>14 correct?</p> <p>15 A Correct.</p> <p>16 Q So --</p> <p>17 A Now I'm saying correct, but I don't</p> <p>18 remember the details that you're quoting. I</p> <p>19 remember the article. I'm -- I -- it doesn't --</p> <p>20 my recollection doesn't contradict anything you're</p> <p>21 saying.</p> <p>22 Q So Venter doesn't tell us anything at</p> <p>23 all about dry talc particles applied externally to</p> <p>24 the genital area being able to migrate up the</p> <p>25 vagina, across the cervix, up the uterus, up the</p>
<p style="text-align: right;">Page 339</p> <p>1 published evidence that talcum powder products and</p> <p>2 its constituents and contaminants that are applied</p> <p>3 to the vaginal area can migrate from there to the</p> <p>4 fallopian tubes and ovaries," citing Venter 1979,</p> <p>5 Henderson 1986, Heller 1996, "or to pelvic lymph</p> <p>6 nodes," citing Cramer 2007.</p> <p>7 Is that correct?</p> <p>8 A Yes, that's correct.</p> <p>9 Q Do you recall, Dr. Siemiatycki, that the</p> <p>10 Venter 1979 article has nothing to do with talc at</p> <p>11 all?</p> <p>12 MS. PARFITT: Objection. Form.</p> <p>13 THE WITNESS: Is that the article about</p> <p>14 asbestos?</p> <p>15 BY MR. KLATT:</p> <p>16 Q Venter 1979 is the article about albumin</p> <p>17 microspheres.</p> <p>18 A Oh, yeah. Yes.</p> <p>19 Q Do you recall that article?</p> <p>20 A I do. Well, I don't recall it well, but</p> <p>21 I recall reading it a year or two ago.</p> <p>22 Q And in Venter, nothing was applied to</p> <p>23 the perineal area, correct? These albumin</p> <p>24 microspheres were actually injected at the top of</p> <p>25 the vaginal vault, correct?</p>	<p style="text-align: right;">Page 341</p> <p>1 fallopian tubes to the ovaries, correct?</p> <p>2 MS. PARFITT: Objection. Form.</p> <p>3 THE WITNESS: I guess I use this as a</p> <p>4 reference because some other experts used it as a</p> <p>5 reference for such a statement. And I read the</p> <p>6 article, and it sounded plausible.</p> <p>7 BY MR. KLATT:</p> <p>8 Q But you'd agree with me that the Venter</p> <p>9 1979 article doesn't involve talc particles,</p> <p>10 doesn't involve external application, and is a</p> <p>11 very artificial situation compared to the</p> <p>12 situation of women applying talc to the --</p> <p>13 MS. PARFITT: Objection.</p> <p>14 BY MR. KLATT:</p> <p>15 Q -- external genital area?</p> <p>16 MS. PARFITT: I'm sorry, Michael.</p> <p>17 Objection. Form.</p> <p>18 THE WITNESS: I -- I -- I don't disagree</p> <p>19 with what you said.</p> <p>20 BY MR. KLATT:</p> <p>21 Q And then the other two articles you</p> <p>22 cite, Henderson 1986 and Heller 1996, say nothing</p> <p>23 at all about migration of talc particles. They</p> <p>24 simply observe talc particles in tissue already</p> <p>25 without any reference to how they got there,</p>

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1 correct?

2 MS. PARFITT: Do you need to see the

3 articles?

4 THE WITNESS: Yes, I think I need to see

5 those articles.

6 MS. PARFITT: Do we have Henderson or

7 Heller?

8 MR. KLATT: I'm sorry, I don't have them

9 with me.

10 MS. PARFITT: Okay. Let's see. In your

11 report -- they're in your report.

12 BY MR. KLATT:

13 Q And you might want to pull Cramer 2007

14 while you're at it, because again my question is

15 the same, it doesn't say anything at all about

16 migration. It simply identifies particles already

17 in tissue without saying how they got there.

18 MS. PARFITT: Okay. Well, let's wait

19 for a question and let's get the articles. Let's

20 see. It would be tab -- it's a big binder.

21 BY MR. KLATT:

22 Q Can I -- can I --

23 THE WITNESS: I have it in my office.

24 BY MR. KLATT:

25 Q Can I short-circuit this?

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1 A Yes.

2 Q I think this -- I can short-circuit

3 this. If you just look at Cramer 2007. Do you

4 have that handy?

5 MS. PARFITT: Cramer 2007. Do you have

6 it? I don't, Michael.

7 THE WITNESS: It would be in my office.

8 MR. KLATT: Could we go off for a second

9 while you are looking?

10 THE VIDEOGRAPHER: We're going off the

11 record at 9:15 p.m.

12 (Pause in the proceedings.)

13 THE VIDEOGRAPHER: We are back on the

14 record at 9:17 p.m.

15 BY MR. KLATT:

16 Q So, Dr. Siemiatycki, at my request,

17 you've pulled the 2007 article, first author

18 Cramer, called "Presence of talc in pelvic lymph

19 nodes of a woman with ovarian cancer and long-term

20 genital exposure to cosmetic talc," correct?

21 A That's correct.

22 Q And my question was simply, this -- this

23 article says nothing about talc migrating. It

24 simply observes that talc was found in a lymph

25 node. Is that correct?

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1 MS. PARFITT: Objection. Form.

2 Make sure you've read the article.

3 THE WITNESS: (Peruses document.) So

4 I -- I've skimmed it quickly. I haven't read

5 everything, but I don't see that it -- sorry, are

6 we on?

7 MS. PARFITT: Yes.

8 THE VIDEOGRAPHER: We're on the record.

9 THE WITNESS: I don't see that it

10 directly addresses talc moving from the vagina

11 into pelvic lymph nodes, but it certainly concerns

12 the detection of talc in pelvic lymph nodes.

13 BY MR. KLATT:

14 Q But it says nothing in the article

15 itself about establishing migration, correct?

16 MS. PARFITT: Objection. Misstates his

17 testimony.

18 BY MR. KLATT:

19 Q That you -- that you see.

20 MS. PARFITT: Objection. Form,

21 misstates his testimony.

22 THE WITNESS: I -- I guess, you know --

23 the question I would have is if it gets to the

24 pelvic lymph nodes, it has to migrate there from

25 somewhere. It's not deposited there deliberately.

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1 BY MR. KLATT:

2 Q Well --

3 A That was my interpretation of -- of

4 this.

5 Q Well, look at the very first page of

6 this article, Cramer. You see at the very top

7 under where the authors are listed?

8 A Yes, I do.

9 Q It says "Background"?

10 A Yeah.

11 Q "Although epidemiologic studies suggest

12 talc use may increase ovarian cancer risk, there

13 is no proof that talc used externally reaches the

14 pelvis." Correct?

15 MS. PARFITT: Objection. Form.

16 BY MR. KLATT:

17 Q That's what it says.

18 A That's the background to this study.

19 That's not --

20 Q And it's 2007, correct?

21 A Correct.

22 Q Which is after the Henderson study that

23 you cite. Correct?

24 A Correct.

25 Q And so after -- and what -- so we have

<p style="text-align: right;">Page 346</p> <p>1 Venter that you cited and Henderson, and what 2 else? 3 A Heller -- Heller? 4 Q What was the third? Heller, yes. Thank 5 you. 1995. And here is -- 6 MS. PARFITT: No, excuse me. 1996, I 7 believe. 8 BY MR. KLATT: 9 Q Excuse me, 1996. 10 And here in 2007, we have Dr. Cramer 11 saying that there's no proof that externally 12 applied talc reaches the ovaries, correct? 13 MS. PARFITT: Objection. Misstates the 14 science and the article and his testimony. Form. 15 BY MR. KLATT: 16 Q I'm just asking what the article -- what 17 Dr. Cramer and Dr. Godleski said in the Background 18 section to this article that you cite in 2007. 19 MS. PARFITT: Objection. Form. 20 THE WITNESS: You want me to comment on 21 whether their background -- the Background section 22 of this abstract contradicts the thesis that there 23 was evidence of migration before 2007? Is that 24 correct? 25 BY MR. KLATT:</p>	<p style="text-align: right;">Page 348</p> <p>1 proof. They haven't -- they didn't say there is 2 no evidence. They said, There is no proof. 3 BY MR. KLATT: 4 Q Do you understand -- my question, 5 Dr. Siemiatycki, was simply, did Dr. Cramer say 6 there was no proof? Correct? 7 MS. PARFITT: Objection. 8 THE WITNESS: He said there was no 9 proof. 10 MS. PARFITT: Asked and answered. 11 THE WITNESS: He didn't say there was no 12 evidence. 13 BY MR. KLATT: 14 Q Okay. Can you go back -- let's see, 15 let's go back to your expert report on biologic 16 plausibility. 17 MS. PARFITT: Right here. 18 BY MR. KLATT: 19 Q Oh, one other thing. When you were just 20 scanning Cramer 2007, I saw you were looking on 21 the page where he discussed the Heller paper. Did 22 you see that? 23 MS. PARFITT: Just give him a moment to 24 get that again. I think it was 17. 25 THE WITNESS: Sorry. No. 17?</p>
<p style="text-align: right;">Page 347</p> <p>1 Q I'm -- my question is, you cited Venter 2 and Henderson and Heller for evidence of 3 migration, correct? 4 A Right. Right. 5 Q And those all predate well before 2007, 6 correct? 7 A Correct. 8 Q And here we have Dr. Cramer saying in 9 2007 there is no proof that talc used externally 10 reaches the pelvis, correct? 11 MS. PARFITT: Objection. Form, 12 misstates the article. 13 BY MR. KLATT: 14 Q Is that what he said? 15 A That's what it says. 16 Q And you -- 17 MS. PARFITT: Wait. Wait. Wait. Wait, 18 you let him finish. He said, That's what he said 19 -- finish, please. Thank you, Michael. 20 THE WITNESS: The -- the word "proof" in 21 that sentence is a red flag. I'm not sure what 22 they mean -- they meant by proof. They might 23 have -- well have said, There is evidence that, 24 but it is not yet conclusive. That is one 25 interpretation of a sentence like, There is no</p>	<p style="text-align: right;">Page 349</p> <p>1 MS. PARFITT: Yeah. 2 THE WITNESS: You have very good eyes if 3 you saw me looking at the Heller. I actually 4 wasn't, but -- 5 BY MR. KLATT: 6 Q I thought you were on that page. 7 A Well, I was -- I scanned each of the 8 four pages. There aren't that many pages. The -- 9 I see mention of the Heller article. 10 Q On page 500? 11 A Yes, I do see that. 12 Q Do you see where Dr. Cramer in 2007 is 13 suggesting that the explanation for the Heller 14 study may be contamination that was introduced 15 during the processing of the tissue specimens? 16 A So I see that he says it might have been 17 introduced during processing, and it's a potential 18 weakness. He doesn't affirm that it is. He says 19 it might be. 20 Q So contamination is another explanation 21 potentially for why you might find talc in ovarian 22 or gynecologic tissues? 23 MS. PARFITT: Objection. Form. 24 THE WITNESS: I -- I guess so. Not 25 being an expert in pathology and physiology, I --</p>

<p style="text-align: right;">Page 350</p> <p>1 that seems like a plausible -- seems to me like a</p> <p>2 plausible alternative explanation.</p> <p>3 BY MR. KLATT:</p> <p>4 Q You go on and comment in the next</p> <p>5 paragraph of your biologic plausibility on two</p> <p>6 trace heavy metals, chromium and nickel compounds,</p> <p>7 correct?</p> <p>8 A So where are we -- oh, yeah. Yes.</p> <p>9 Q You're aware that IARC has made</p> <p>10 determinations regarding chromium and nickel</p> <p>11 compounds, correct?</p> <p>12 A Yes, correct.</p> <p>13 Q And neither one of the determinations</p> <p>14 found they were linked to ovarian cancer at all,</p> <p>15 correct?</p> <p>16 A That's correct.</p> <p>17 Q They found they were related to nasal,</p> <p>18 sinus and lung cancers in people, primarily</p> <p>19 workers, who had breathed the fumes, correct?</p> <p>20 A That's correct.</p> <p>21 Q So that's no way analogous to any trace</p> <p>22 heavy metals in talc, correct?</p> <p>23 MS. PARFITT: Objection. Form.</p> <p>24 THE WITNESS: It's -- it's not directly</p> <p>25 relevant. It may be indirectly relevant. The</p>	<p style="text-align: right;">Page 352</p> <p>1 THE VIDEOGRAPHER: This ends -- this</p> <p>2 ends the deposition of Jack Siemiatycki.</p> <p>3 We are going off the record at 9:28 p.m.</p> <p>4 (Whereupon, the deposition</p> <p>5 of JACK SIEMIATYCKI, Ph.D. was</p> <p>6 concluded at 9:28 p.m.)</p> <p>7</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>
<p style="text-align: right;">Page 351</p> <p>1 evidence that allowed IARC to make determinations</p> <p>2 about lung cancer risks is evidence from</p> <p>3 industrial cohorts of males.</p> <p>4 And so there has never been an</p> <p>5 evaluation of ovarian cancer risks in relation to</p> <p>6 exposed women to chromium and nickel. It's terra</p> <p>7 incognita basically.</p> <p>8 BY MR. KLATT:</p> <p>9 Q And so following up on that, you're not</p> <p>10 aware of any evidence at all that women who have</p> <p>11 used externally applied talcum powder to the</p> <p>12 genital area have higher blood or tissue levels of</p> <p>13 chromium or nickel compounds than women who've</p> <p>14 never ever used talc at all, correct?</p> <p>15 MS. PARFITT: Objection. Form.</p> <p>16 THE WITNESS: I've -- I'm not aware of</p> <p>17 any evidence.</p> <p>18 MR. KLATT: I think that's all the</p> <p>19 questions I have.</p> <p>20 MS. PARFITT: I have no further</p> <p>21 questions.</p> <p>22 Dr. Siemiatycki, you are done. We will</p> <p>23 read and sign.</p> <p>24 Thank you, Leslie.</p> <p>25 Thank you all.</p>	<p style="text-align: right;">Page 353</p> <p>1 CERTIFICATE OF CERTIFIED SHORTHAND REPORTER</p> <p>2 The undersigned Certified Shorthand Reporter</p> <p>3 does hereby certify:</p> <p>4 That the foregoing proceeding was taken before</p> <p>5 me at the time and place therein set forth, at</p> <p>6 which time the witness was duly sworn; That the</p> <p>7 testimony of the witness and all objections made</p> <p>8 at the time of the examination were recorded</p> <p>9 stenographically by me and were thereafter</p> <p>10 transcribed, said transcript being a true and</p> <p>11 correct copy of my shorthand notes thereof; That</p> <p>12 the dismantling of the original transcript will</p> <p>13 void the reporter's certificate.</p> <p>14 In witness thereof, I have subscribed my name</p> <p>15 this date: February 4, 2019.</p> <p>16</p> <p>17 _____</p> <p>18 LESLIE A. TODD, CSR, RPR</p> <p>19 Certificate No. 5129</p> <p>20</p> <p>21 (The foregoing certification of</p> <p>22 this transcript does not apply to any</p> <p>23 reproduction of the same by any means,</p> <p>24 unless under the direct control and/or</p> <p>25 supervision of the certifying reporter.)</p>

## INSTRUCTIONS TO WITNESS

Please read your deposition over carefully and make any necessary corrections. You should state the reason in the appropriate space on the errata sheet for any corrections that are made.

After doing so, please sign the errata sheet and date it.

You are signing same subject to the changes you have noted on the errata sheet, which will be attached to your deposition. It is imperative that you return the original errata sheet to the deposing attorney within thirty (30) days of receipt of the deposition transcript by you. If you fail to do so, the deposition transcript may be deemed to be accurate and may be used in court.

## ERRATA

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## ACKNOWLEDGMENT OF DEPONENT

I, \_\_\_\_\_, do hereby certify that I have read the foregoing pages, and that the same is a correct transcription of the answers given by me to the questions therein propounded, except for the corrections or changes in form or substance, if any, noted in the attached Errata Sheet.

JACK SIEMIATYCKI, Ph.D.

DATE

Subscribed and sworn to before me this

\_\_\_\_\_ day of \_\_\_\_\_, 20\_\_\_\_.

My commission expires: \_\_\_\_\_

Notary Public

# Exhibit 146

## **Interpretation of Epidemiologic Studies on Talc and Ovarian Cancer**

prepared by

Kenneth J. Rothman  
Harris Pastides  
Jonathan Samet

November 28, 2000

### **Executive Summary**

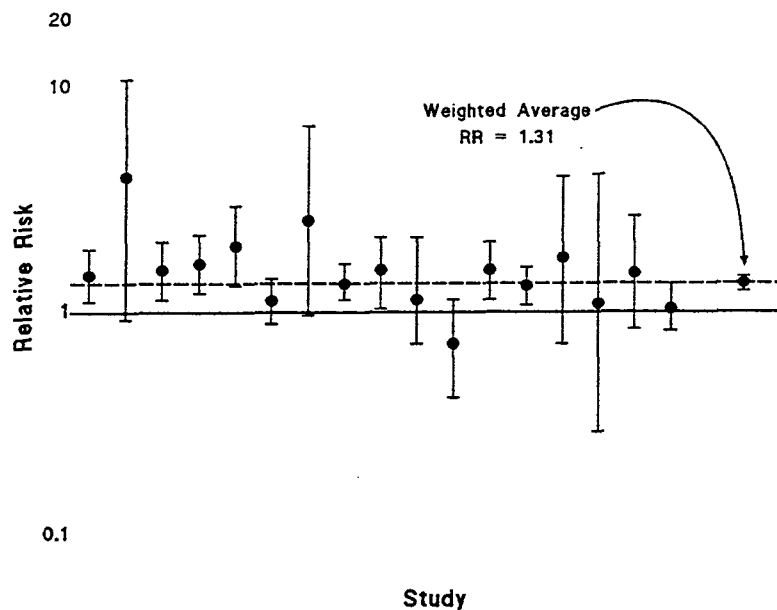
A weighted average of the results from epidemiologic studies to date measuring the relation between talc and ovarian cancer risk gives an overall relative risk of 1.31, with a 95% confidence interval of 1.21–1.41. Bias and causation are competing explanations for the weak positive association observed. This weak association could be an underestimate of a stronger association if there are errors in measuring talc exposure that apply uniformly to all study subjects (nondifferential misclassification). On the other hand, nondifferential misclassification does not bias an association that is null to begin with, so postulating nondifferential misclassification cannot shed light on whether the association results from a causal relation or not. Most of the published studies are interview-based case-control studies, subject to recall bias, which can readily give rise to associations of this magnitude. The evidence from these studies regarding recall bias is mixed. Uncontrolled confounding can also easily explain associations this weak; although no single confounding factor would seem to account for the overall effect, the combined effect of several such unidentified confounders could do so. In considering these competing explanations of bias and causation, the evidence in favor of a causal explanation is only the overall weak association of a relative risk of 1.31. The lack of a plausible biologic mechanism, on the other hand, weighs against a causal interpretation. Also weighing against a causal explanation is the dose-response pattern among talc users, which is an inverse trend for both duration of use and frequency of use. A causal relation would predict a positive trend, not an inverse trend. Based on these considerations, we suggest that the evidence to date does not indicate that talc can be "reasonably anticipated to be a human carcinogen."

## Introduction

In this document we offer an interpretation of the epidemiologic literature with respect to the causal hypothesis that talc exposure causes an increase in the occurrence of ovarian cancer. Overall, we identified 23 epidemiologic studies conducted since 1980 that have examined consumer talc exposure with respect to subsequent risk for ovarian cancer.<sup>1-23</sup> The search methodology is described in the appendix. Sixteen of these were case-control studies reporting new data with effect estimates for talc exposure,<sup>2-5,7,10,11,13-15,17-19,21-23</sup> and one was a cohort study reporting an effect estimate.<sup>9</sup> One study examined occupational exposure to talc in women, but there were few exposed women in this study<sup>16</sup>; the other studies did not report quantitative effect estimates. The importance of this comparatively small set of epidemiologic studies is underscored by the paucity of relevant animal research on this question.

Most of these published reports come from epidemiologic studies in which talc was not the primary focus. Perhaps for this reason, talc exposure information was often crude. In only a few of these studies was there any attempt to categorize talc exposure by frequency of use or duration of use. For the 17 studies that reported some epidemiologic measure of effect, it was usually a relative risk estimate for ovarian cancer given that there was some exposure to talc, compared with no exposure or minimal exposure. These results are depicted graphically in figure 1. The findings on balance indicate a slight positive association between talc exposure and ovarian cancer, with an overall weighted relative risk of 1.31, and a 95% confidence interval of 1.21–1.41.

**Figure 1**  
**Study-specific Relative Risk Estimates for Ovarian Cancer Among Talc Users,**  
**and Overall Weighted Average of Study Results**



**Issues Affecting Causal Inference**

Inferring a causal relation from a pattern of epidemiologic results follows no recipe, but certain principles can be applied. To begin with, what alternative explanations might be offered to explain a pattern of positive findings? If an uncontrolled confounding factor or a study-related bias could explain the results, a causal inference is less reasonable. Second, is there a plausible biologic mechanism? For example, environmental tobacco smoke shows a weak association with lung cancer in numerous epidemiologic studies of never smokers, but the plausibility of the relation, based on the known constituents of the smoke and their effect in higher concentrations, among active smokers, makes a causal inference more reasonable. Third, is there a consistent dose-response trend in the data? With rare exception, every causal relation in epidemiologic research shows a progressive relation between various measures of increasing exposure. In this discussion paper, we address the following issues that we believe are potentially relevant to causal inference regarding talc and ovarian cancer:

1. Exposure misclassification
2. Recall bias
3. Confounding
4. Dose-response trends
5. Biologic mechanism

Below we discuss briefly the import of each of these topics with respect to the interpretation of the epidemiologic literature of talc and ovarian cancer. We omit discussion of the role of chance in explaining any of the findings, because the combined weight of the 17 studies in figure 1 indicates that chance alone is an unlikely explanation for the overall weighted average of relative risks from the studies of 1.31. Other possible issues, such as selection biases and reverse causation might be relevant, but appear less important to us in interpreting these results, so we have omitted them in the interests of brevity. (Reverse causation, for example, could occur if preclinical ovarian cancer prompted women to use talc; while this situation is possible in some instances, we do not think it is a realistic explanation for the observed effects.)

**Exposure Misclassification**

Nearly all the studies were case-control studies. It is commonly believed that the validity of case-control studies is worse than that of cohort studies, but this view is mistaken. The validity of a study depends on the specifics of the study design, the nature of the data, and the nature of the hypothesis that the study addresses. For example, a cohort study that examines the long-term risk of cancer among coffee drinkers after a one-time dietary assessment of coffee consumption would suffer from weak exposure assessment. Although the exposure information might be accurate for the time at which it was collected, the exposure status of cohort members will change with time and the initial measure might be only poorly correlated with a more meaningful measure of coffee consumption. The effect of having a poor measure of exposure will be considerable nondifferential misclassification, a type of error that introduces a bias into study results that tends to drive effect estimates towards the null condition of no effect. In contrast, it may be possible to get more detailed exposure information from study subjects in a case-control study, which might thus avoid some of the bias that would result from a cohort study.

Much like coffee consumption, talc exposure is likely to vary over time as women age and their reasons for deciding to use talc change. Consequently a single baseline assessment of talc exposure at the start of follow-up in a cohort may lead to effect estimates that are biased toward the null. If talc habits are steady over time, a single baseline assessment becomes more informative. Furthermore, if talc use influences cancer risk with a long induction period, talc assessment at the start of a cohort study is more meaningful than an assessment of coffee drinking on heart disease risk, which is thought to have only a short-term effect.

Case-control studies also suffer from exposure misclassification, but the potential exists to extract more detailed history of exposure from the subject interview. In most of these studies, the exposure metric is based on interview information. It is subject to inaccuracies from recall error, as well as inaccuracies reflecting the nature of the questions asked and their relation to any biologically relevant measure of talc exposure. Ideally one would wish to have a measure of talc dose within the upper reproductive tract. The actual measures obtained by interview, however, are likely to be only modestly correlated with a hypothetically ideal measure. The result of this inevitable non-differential misclassification would be to bias any real effect towards the null. Nevertheless, one cannot draw the conclusion that the overall slight positive relation between talc exposure and ovarian cancer must be an underestimate of a larger effect because of nondifferential misclassification. Non-differential misclassification does not introduce any bias toward the null if the association is null to begin with, so to draw the conclusion that the overall effect estimate from the 17 studies is an underestimate, one must already know or assume that there is an even stronger positive relation in the data. Thus, the prospect of non-differential misclassification in measuring talc exposure does not provide any help by itself in assessing whether talc is related to ovarian cancer.

### **Recall Bias**

Cohort studies do not suffer from recall bias, but recall bias is an issue for case-control studies that obtain exposure information from subject interviews. Such was the case for all the case-control studies whose effects are summarized in figure 1. Recall bias can readily introduce enough bias to produce the modestly-sized overall effect ( $RR = 1.3$ ) that emerges from these studies. As an example, one of us reported an association between Bendectin and congenital heart disease in 1979, with a  $RR$  of 1.6.<sup>24</sup> One possibility for that positive relation was recall bias, a strong consideration in light of the study design that produced the finding (the study was not designed to evaluate Bendectin, which was only an incidental finding). To resolve the issue, a second study was undertaken, this time aimed at evaluating an effect of Bendectin by eliminating recall bias using a different design.<sup>25</sup> The second study found a  $RR$  of 1.0, prompting the conclusion that the  $RR$  of 1.6 reported in the earlier study was due to recall bias. The amount of recall bias for Bendectin in the 1979 study amounted to an apparent effect that was much stronger than the overall effect estimate for talc and ovarian cancer in the combined studies in figure 1.

We believe that there is mixed evidence for recall bias in these studies. We base this interpretation on the few studies that examined the effect of talc separately among women who had a tubal ligation and those who did not. If recall bias were the explanation for the full effect seen in the published literature, we would predict that the effect of talc exposure would appear to be about the same for women who have a tubal ligation and those who did not, because tubal ligation is unlikely to affect recall bias. In contrast, it would likely affect any biologic action of

talc. Only three studies give information relevant to this question. In those studies, the evidence is mixed. In one study the effect of talc is greater among women who have not had a tubal ligation,<sup>22</sup> and in a second, talc use appeared to have no adverse effect among women who had either a hysterectomy or a tubal ligation.<sup>23</sup> In the third study,<sup>2</sup> however, there was little difference in the effect of talc for women with and without tubal ligation or hysterectomy and the effect for both groups was near null. Thus, the overall evidence on the possibility of recall bias is equivocal, with no clear answer as to whether recall bias can be eliminated as an explanation.

### Confounding

Although there are some strong risk factors for ovarian cancer, for any of them to be confounding to an extent that could account for the positive relations that have been reported, they would have to be strongly correlated with talc use. Family history, ethnicity, obesity and some reproductive risk factors are positively associated with the risk of ovarian cancer, but the magnitude of these associations does not appear high enough to introduce enough confounding, even jointly, to explain completely the positive association. Of course, it remains possible that yet unidentified risk factors for ovarian cancer could be important confounders, and several such factors in the aggregate could give risk to an overall association as weak as the one between talc and ovarian cancer.

### Dose-response trends

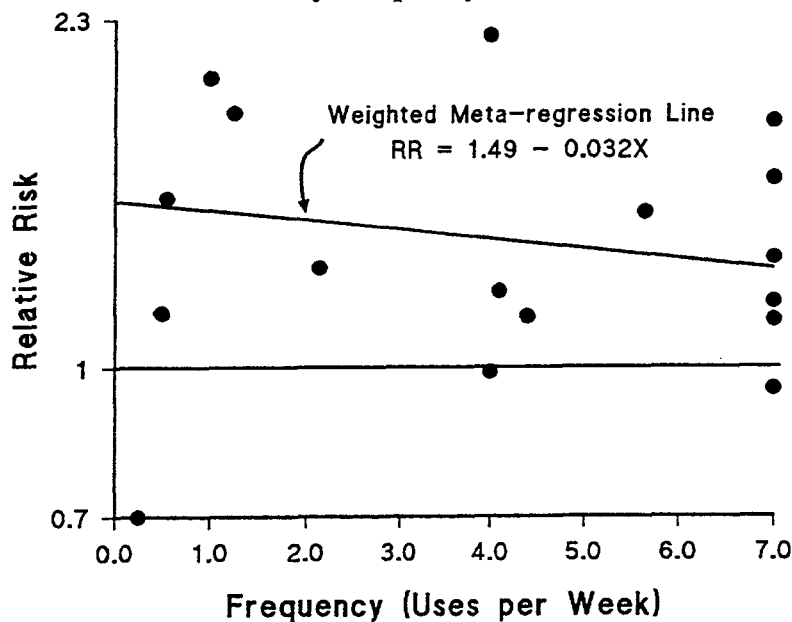
A nearly constant feature of causal relations in epidemiology and in the pathogenesis of cancer in particular is a monotonically increasing relation between measures of exposure and disease risk. Even when disease risk increases through a threshold phenomenon, progressive dose-response trends are observed because the exposure measure varies and smooths the step relation of a threshold into a gradual climb in risk. In contrast, many biases would not produce a monotonic dose-response relation. For example, Horwitz and Feinstein advanced a theory of "detection-bias" as a non-causal alternative to the theory that exogenous estrogens cause endometrial cancer.<sup>26</sup> According to this theory, administration of estrogens would provoke genital bleeding among some women, leading to a work up and to the diagnosis of pre-existing endometrial cancers, accounting for the observed association. This theory, however, predicted that the increase in endometrial cancer risk would be greatest for short-term users of exogenous estrogens and would decline toward no effect for longer-term users. In actual fact this inverse dose-response trend was not observed, undermining the detection bias theory.

Exposure to talc can be characterized by the age at which use started, the number of years of use, and the frequency of use (e.g., number of times per day or per week). Among the talc studies, several reported on either frequency of talc use or duration of talc use, or both. We combined the findings from these studies into a meta-regression,<sup>27</sup> an analysis that combines dose-specific information from various studies into a single weighted regression analysis. Each data point in a meta-regression represents one effect estimate at a given dose level; the data points are weighted by the precision of each estimate, back-calculated from the confidence interval for that estimate.

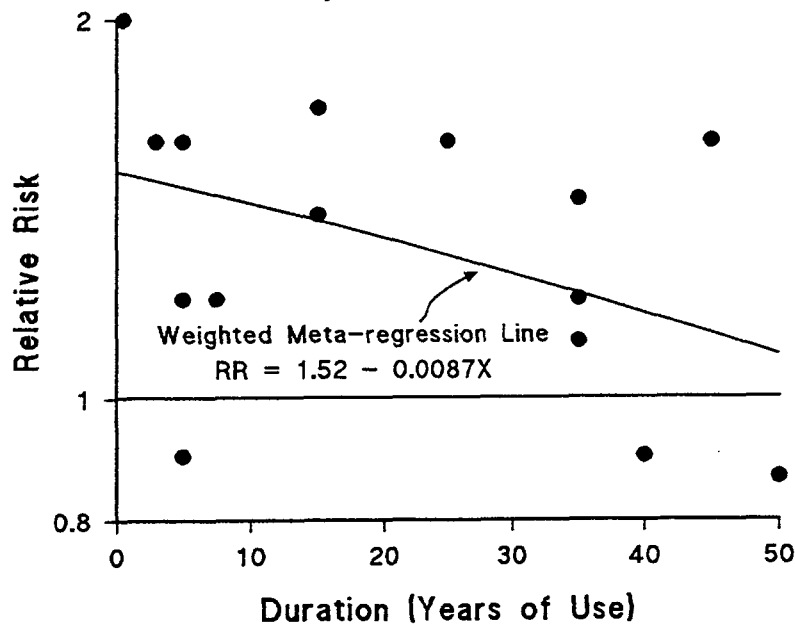
In figure 2 we show the data points and meta-regression line for frequency of talc use, and in figure 3 for duration of talc use. These regression analyses confirm the picture that one obtains from reading the individual studies (table 1): the dose-response relation across dose levels above zero for talc exposure is not increasing, but instead declines. Although

misclassification could flatten a dose-response curve, it would not produce an inverse dose-response curve. Thus, the observed pattern, whether based on individual studies or from the combined meta-regression analysis, is not consistent with a causal interpretation for talc exposure. Instead it suggests that some as yet unidentified bias accounts for the overall modest relation between talc exposure and ovarian cancer.

**Figure 2**  
**Trend in Relative Risk by Frequency of Talc Use Among Users**



**Figure 3**  
**Trend in Relative Risk by Duration of Talc Use Among Users**



**Table 1**  
**Relative Risk Estimates of Ovarian Cancer by Frequency and Duration of Talc Use\***

<b>Citation</b>	<b>Frequency (Applications/wk)</b>	<b>Relative Risk</b>	<b>95% Confidence Interval</b>
Booth et al.1989	7.00	1.30	0.80-1.90
	1.00	2.00	1.30-3.40
	0.25	0.70	0.30-1.80
Chang and Risch 1997	1.25	2.00	1.24-2.73
	4.40	1.13	0.74-1.72
	7.00	0.95	0.61-1.49
Cramer et al. 1999	4.00	2.21	1.37-3.56
	7.00	1.17	0.78-1.76
	7.00	1.57	0.80-3.10
Gertig et al. 2000	0.50	1.14	0.81-1.59
	4.00	0.99	0.67-1.46
	7.00	1.12	0.82-1.55
Harlow et al. 1992	0.55	1.50	0.80-2.70
	4.10	1.20	0.60-2.20
	7.00	1.80	1.10-3.00
Whittemore et al. 1988	2.14	1.27	0.82-1.96
	5.65	1.45	0.94-2.22

<b>Citation</b>	<b>Duration (years)</b>	<b>Relative Risk</b>	<b>95% Confidence Interval</b>
Chang and Risch 1997	15	1.70	1.09-2.64
	35	1.44	0.96-2.15
	50	0.86	0.54-1.38
Harlow et al. 1992	5	1.20	0.50-2.60
	25	1.60	1.00-2.70
	45	1.60	1.00-2.70
Ness et al. 2000	1	2.00	1.00-4.00
	3	1.60	1.10-2.30
	7.5	1.20	0.80-1.90
	35	1.20	1.00-1.50
Whittemore et al. 1988	5	1.60	1.00-2.57
	35	1.11	0.74-1.65
Wong et al. 1999	5	0.90	0.60-1.50
	15	1.40	0.90-2.20
	40	0.90	0.60-1.20

\* For Open-ended Categories, the Values Assigned Assume that the Upper Category Boundary Corresponds to a Maximum Frequency Equal to Daily Use and a Maximum Duration of Use of 60 Years

**Biologic Mechanism**

The most plausible biological mechanism relating to the development of ovarian cancer concerns ovulation and the hormonal factors affecting it. Specifically, factors that suppress ovulation, such as gravidity, breast feeding, oral contraceptive use, tubal ligation and hysterectomy appear to reduce strongly the risk of ovarian cancer. Body mass index may also affect ovarian cancer risk. Medical conditions that may affect ovulation and also appear to increase the risk of ovarian cancer include endometriosis, ovarian cysts, and hyperthyroidism.

It does not appear plausible, however, that talc exposure has a direct effect on ovulation. If talc exposure is correlated with factors that affect ovulation, that correlation would produce confounding, as discussed above. If talc were a cause of ovarian cancer, it is presumably through a different mechanism than the many risk factors already known to affect ovarian cancer risk. There is no other evidence regarding such a mechanism, nor any clear evidence that talc applied perineally or on diaphragms makes its way physically to the ovaries. Ness et al suggest that inflammation may mediate ovarian cancer risk and that talc may play a role by causing inflammation.<sup>17</sup> This theory merits further investigation, although the tenability of the theory rests on the issue of whether talc particles physically reach the ovaries. Without a clear biologic mechanism for talc to cause ovarian cancer, an inference that talc does cause ovarian cancer would be an example of a "black-box" inference, meaning that the inference lacks a biologic foundation. "Black-box" inferences, such as the inference some draw that electromagnetic fields increase the risk for various cancers, are not necessarily invalid, but they are inherently more tenuous than inferences that are rooted in biologic explanations.

**Conclusion**

The only evidence to support a causal interpretation is the overall modest positive association seen in most of the epidemiologic studies that we have cited. The association is weak enough to be plausibly explained by unidentified bias. Recall bias is one possibility, but unidentified confounding could also readily give rise to the weak level of association that confronts us from these studies. Bias and causation are competing explanations for the weak positive association observed, an association that could be an underestimate of a stronger real association if nondifferential misclassification has diluted it. In considering these competing explanations, the lack of a plausible biologic mechanism based on the evidence to date weighs against a causal interpretation. More important, there is also positive evidence against a causal association: the inverse dose-response trend for both duration of use and frequency of use, a pattern that could not be explained by a causal relation. Based on these considerations, we suggest that the evidence to date does not indicate that talc can be "reasonably anticipated to be a human carcinogen."

## References

1. Booth M, Beral V, Smith P: Risk factors for ovarian cancer: A case-control study. *Br J Cancer* 1989;60:592-598.
2. Chang S, Risch HA: Perineal talc exposure and risk of ovarian carcinoma. *Cancer* 1997;79:2396-2401.
3. Chen Y, Wu PC, Lang JH, Ge WJ, Hartge P, Brinton LA: Risk factors for epithelial ovarian cancer in Beijing, China. *Int J Epidemiol* 1992;21:23-29.
4. Cook LS, Kamb ML, Weiss NS: Perineal powder exposure and the risk of ovarian cancer. *Am J Epidemiol* 1997;145:459-465.
5. Cramer DW, Liberman RF, Titus-Ernstoff L, Welch WR, Greenberg ER, Baron JA, Harlow BL: Genital talc exposure and risk of ovarian cancer. *Int J Cancer* 1999; 81:351-356.
6. Cramer DW, Xu H: Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. *Ann Epidemiol* 1995;5:310-314.
7. Cramer DW, Welch WR, Scully RE, Wojciechowski CA: Ovarian cancer and talc. *Cancer* 1982;50:372-376.
8. Eltabbakh GH, Piver MS, Natarajan N, Mettlin CJ: Epidemiologic differences between women with extraovarian primary peritoneal carcinoma and women with epithelial ovarian cancer. *Obstet Gynecol* 1998;91:254-259.
9. Gertig DM, Hunter DJ, Cramer DW, Colditz GA, Speizer FE, Willett WC, Hankinson SE: Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst* 2000;92:249-252.
10. Godard B, Foulkes WD, Provencher D, Brunet JS, Tonin PN, Mes-Masson AM, Narod SA, Ghadirian P: Risk factors for familial and sporadic ovarian cancer among French Canadians: A case-control study. *Am J Obstet Gynecol* 1998;179:403-410.
11. Green A, Purdie D, Bain C, Siskind V, Russell P, Quinn M, Ward B, and the Survey of Women's Health Study Group: Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. *Int J Cancer* 1997;71:948-951.
12. Hankinson SE, Hunter DJ, Colditz GA, Willett WC, Stampfer MJ, Rosner B, Hennekens CH, Speizer FE: Tubal ligation, hysterectomy, and risk of ovarian cancer. A prospective study. *JAMA* 1993;270:2813-2818.

13. Harlow BL, Cramer DW, Bell DA, Welch WR: Perineal exposure to talc and ovarian cancer risk. *Obstet Gynecol* 1992; 80:19-26.
14. Harlow BL, Weiss NS: A case-control study of borderline ovarian tumors: The influence of perineal exposure to talc. *Am J Epidemiol* 1989;130:390-394.
15. Hartge P, Hoover R, Leshner LP, McGowan L: Talc and ovarian cancer. *JAMA* 1983;250:1844.
16. Hartge P, Stewart P: Occupational and ovarian cancer: A case-control study in the Washington, DC, metropolitan area, 1978-1981. *J Occup Med* 1994;36:924-927.
17. Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, Morgan M., Schlesselman JJ: Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology* 2000;11:111-117.
18. Purdie D, Green A, Bain C, Siskind V, Ward B, Hacker N, Quinn M, Wright G, Russell P, Susil B: Reproductive and other factors and risk of epithelial cancer: An Australian case-control study. Survey of Women's Health Study Group. *Int J Cancer* 1995;62:678-684.
19. Rosenblatt KA, Szklo M, Rosenshein NB: Mineral fiber exposure and the development of ovarian cancer. *Gynecol Oncol* 1992;45:20-25.
20. Shushan A, Paltiel O, Iscovich J, Elchalal U, Peretz T, Schenker J: Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertil Steril* 1996;65:13-18.
21. Tzonou A, Polychronopoulou A., Hsieh CC, Rebelakos A, Karakatsani A, Trichopoulos D: Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int J Cancer* 1993;55:408-410.
22. Whittemore AS, Wu ML, Paffenbarger RS, Sarles DL, Kampert JB, Grosser S, Jung DL, Ballon S, Hendrickson M: Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am J Epidemiol* 1988;128:1228-1240.
23. Wong C, Hempling RE, Piver MS, Natarajan N, Mettlin CJ: Perineal talc exposure and subsequent epithelial ovarian cancer: A case-control study. *Obstet Gynecol* 1999;93:372-376.
24. Rothman KJ, Fyler DC, Goldblatt A, Kreidberg MB: Exogenous hormones and other drug exposures of children with congenital heart disease. *Am J Epidemiol* 1979;109:433-439.

25. Zierler S, Rothman KJ: Congenital heart disease in relation to maternal use of Bendectin and other drugs in early pregnancy. *N Engl J Med* 1985;313:347-352.
26. Horwitz RI, Feinstein AR: Alternative analytic methods for case-control studies of estrogens and endometrial cancer. *N Engl J Med*. 1978;299:1089-94.
27. Maclure M: Demonstration of deductive meta-analysis: ethanol intake and risk of myocardial infarction. *Epidemiol Rev*. 1993;15:328-51.

## **Appendix**

### **Literature Search Methodology**

The literature search was designed to find published epidemiologic studies specifically relating to the perineal use of non-asbestiform talc. The 2000 NTP Draft Report was used as the initial resource to locate applicable studies. To identify other relevant publications, an on-line search was performed in Dialog and using the internet. In addition, medical and scientific resources such as Medline, Toxline, and SciSearch were queried using various keyword terms including "talc," "non-asbestiform," "ovarian cancer," and "perineal." The search was limited to papers published after 1980, because asbestiform products were removed from the market in 1976. Once relevant articles were obtained, bibliographies were "tree-searched" to identify other applicable studies that may have been omitted during the on-line search. "Tree-searching" involves reading an article's bibliography, and then identifying citations that may contain appropriate information based on the title or author. "Tree-searching" identified early studies or those not recorded in on-line databases.

# Exhibit 147

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

**IN RE: JOHNSON & JOHNSON TALCUM POWDER  
PRODUCTS MARKETING, SALES PRACTICES AND  
PRODUCTS LIABILITY LITIGATION**

***THIS DOCUMENT RELATES TO ALL CASES***

**MDL NO. 16-2738 (FLW) (LHG)**

**EXPERT REPORT OF KARLA BALLMAN, Ph.D.  
FOR GENERAL CAUSATION *DAUBERT* HEARING**

Date: February 25, 2019

A handwritten signature in black ink that reads "Karla V. Ballman". The signature is written in a cursive, flowing style. Below the signature is a horizontal line.

Karla Ballman, Ph.D.

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## 1 MY QUALIFICATIONS

I am the Chief of the Division of Biostatistics and Epidemiology at Weill Cornell Medicine as well as a tenured Professor of Biostatistics in the Department of Healthcare Policy and Research. I have been working in cancer research for more than 19 years.

I received a BA degree from Macalester College in St. Paul, Minnesota with a double major in economics and mathematics. Subsequently, I received a Master's degree (S.M.) and Ph.D. in Operations Research from the Massachusetts Institute of Technology. A degree in Operations Research includes substantial training in statistics and epidemiology.

Upon receiving my degree, I was hired as a faculty member (Assistant Professor) at Macalester College to develop an undergraduate statistics curriculum and to teach statistics courses. I also was a faculty member of the Department of Statistics at the University of Auckland in New Zealand where I taught several statistics and epidemiology courses. Upon returning to the United States, I took a position at Mayo Clinic (Rochester, Minnesota) in the Division of Biostatistics and was a member of the Mayo Comprehensive Cancer Center. While at Mayo, I served as the Chair of the Division of Biostatistics and attained the rank of Professor. At Mayo, I was involved in hundreds of clinical research studies including clinical trials and observational studies. I left Mayo more than three years ago to assume the position of the Division Chief within the Department of Healthcare Policy & Research at Weill Cornell Medicine.

Over the years, I have collaborated with investigators on numerous observational studies and clinical trials. I ensure that the study design is scientifically rigorous, that the data are appropriate and of high quality, and that interpretations made are supported by the data. This work is funded primarily through peer-reviewed government grants and peer reviewed foundation grants. I am a co-investigator on numerous grants that fund cancer projects and am a co-author on more than 200 manuscripts, most of which are related to cancer research.

I have many other positions and responsibilities relevant to cancer. I serve as a Deputy Editor for the Journal of Clinical Oncology (JCO), one of the top cancer journals in the world. In this role, I obtain reviewers for submitted manuscripts that are assigned to me and evaluate whether the manuscripts are of sufficient priority for publication based on the novelty of their findings and the scientific rigor of the study design and analyses. I am responsible for the evaluation of an average of ten manuscripts per week. As a Deputy Editor, I am also consulted on manuscripts handled by Associate Editors regarding their suitability and priority for publication in JCO. Most of the manuscripts I personally handle involve assessing risk factors across a range of cancers. I also serve on numerous scientific review panels that evaluate proposals submitted for potential funding. My role on these panels is to assess proposals for their scientific rigor and their potential impact on cancer outcomes. Over the years, I have

served on more than 65 grant review panels. These include panels for government funding including the National Cancer Institute, the National Institutes of Health and Department of Defense Congressionally Directed Medical Research Programs as well as those for foundation funding such as the Damon Runyon Cancer Research Foundation and the Sarcoma Alliance for Research through Collaboration (SARC) foundation.

As mentioned, I have co-authored more than 200 peer-reviewed manuscripts, most of which address cancer-related issues. The cancer areas in which I have worked include breast cancer, prostate cancer, brain cancer, cancer in the elderly, lung cancer, sarcoma, and melanoma. The types of studies in which I have been an active collaborator include clinical trials, cancer biomarkers, and observational studies for cancer risk factors or cancer prognostic factors. My contributions include devising scientifically rigorous study designs aligned with the study objectives, performing appropriate analyses, and ensuring the interpretation of the data and subsequent conclusions are supported by the data.

Throughout my career, I have taught formal and informal courses in statistics and epidemiology for, and mentored participants in, advanced degree and postdoctoral programs.

I am being compensated at a rate of \$400 per hour for my expert work in this litigation. All of the opinions in this report are stated to a reasonable degree of scientific certainty. My curriculum vitae is attached to this report, together with other required disclosures.

## 2 SUMMARY OF OPINIONS

### 2.1 STUDY DESIGNS

Epidemiological studies may be designed in a number of ways, and design affects the weight the study should be accorded in undertaking a global assessment of the available evidence. In ascending order of weight (for reasons I elaborate below), the studies I address are case reports and case studies; case-control studies; prospective cohort studies; and randomized critical trials. My focus in this report is on case-control studies and prospective cohort studies due to the very limited value of case reports and the absence of randomized critical trials concerning talcum powder exposure and ovarian cancer.

### 2.2 META-ANALYSIS

The term “meta-analysis” when broadly defined encompasses a range of methodological approaches for synthesizing the results of multiple individual studies. These methods include systematic reviews, pooled studies, and true meta-analyses. In this report I focus on pooled studies (which synthesize the underlying, individual patient data from published studies) and

meta-analyses (which synthesize the summary results of the individual studies and do not incorporate individual patient data) that have been performed with respect to exposure to talcum powder and ovarian cancer.

## 2.3 THE BRADFORD HILL FRAMEWORK

The Bradford Hill framework affords a widely accepted methodology for attempting to determine whether an association reported in the epidemiological literature reflects a causal relationship between an exposure and outcome of interest. That framework considers the epidemiological data themselves – including strength and consistency of the reported association and the existence of a dose-response relationship – as well as other considerations, including the biological plausibility of the posited relationship, the temporal relationship between exposure and disease and other factors.<sup>1</sup>

## 2.4 THE LACK OF SUPPORT FOR A CAUSAL CONCLUSION WITH RESPECT TO TALCUM POWDER EXPOSURE AND OVARIAN CANCER

In applying the Bradford Hill criteria to this context, I conclude that the evidence does not support the conclusion that cosmetic talcum powder use causes ovarian cancer. The reported association is weak, meaning that a strong demonstration of the other factors would be required to support a causal conclusion; however, no such strong showing can be demonstrated. The association reported is inconsistent, and very few studies have reportedly found a dose-response relationship. The proposed biological mechanisms by which talcum powder would cause ovarian cancer are underdeveloped and either contradicted by, or not supported by, lines of evidence that should, in the current state of cancer research, be well developed if the posited causal relationship were real. Other Bradford Hill considerations also do not support the causal hypothesis.

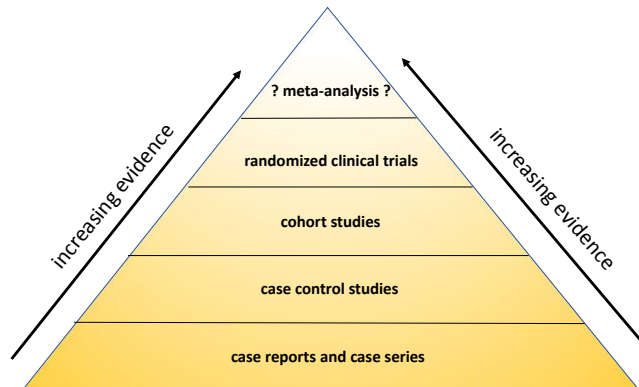
## 2.5 ADDITIONAL PROBLEMS WITH THE CAUSAL HYPOTHESIS

I also find that additional considerations support the conclusion that sufficient evidence for a causal relationship is lacking. I consider and reject the possibility, for example, that the epidemiological data lend further support for a causal relationship with the serous subtype of ovarian cancer. In addition, I identify several considerations that show that the best explanation for the different findings in cohort and case-control studies is that case-control studies are driven by bias and confounding. Additionally, I evaluate the evidence that has been developed since the International Agency for Research on Cancer (IARC) issued its working paper on talcum powder and show that the subsequently developed evidence only further supports the conclusion that the evidence is insufficient to support a causal relationship between talcum powder use and ovarian cancer.<sup>2</sup>

### 3 STUDY DESIGNS

There are different study designs used in epidemiology, each type with its own degree of evidence. Figure 1 illustrates the level of evidence within each trial design with increasing evidence moving up the pyramid. Each of the study designs is discussed below.

FIGURE 1: RELATIVE AMOUNT OF EVIDENCE FOR CAUSALITY BY STUDY DESIGN<sup>1</sup>



#### 3.1 CASE REPORTS AND CASE SERIES

The least amount of evidence provided for a cause-and-effect relationship is provided by a case report. A case report describes a single case or two and is considered to be anecdotal in nature. In medicine, a case report provides details for an individual patient such as treatment and subsequent outcome or past exposure to an agent and the subsequent development of disease. Case reports usually describe an unusual or novel occurrence and are shared for educational purposes. By their nature, they focus on rare, unusual occurrences and are used to generate hypotheses rather than provide definitive proof of a causal relationship. Case reports by their nature are not reflective of statistical sampling from the general population. As a consequence, they are placed at the bottom of the clinical evidence hierarchy. The major value of case reports is in uncovering new diseases or rare adverse effects of treatments.

A case series identifies subjects with a known exposure and reports on subsequent outcomes. Case series may be comprised of a consecutive series of patients or a selected subsample. The sample size is generally small and only includes individuals who were exposed or treated; there

<sup>1</sup> The question marks around meta-analysis in Figure 1 reflect the fact that there is some disagreement as to whether meta-analyses are the highest level of evidence. It should be noted that in this figure, the meta-analysis refers to the pooling of randomized clinical trials results. A meta-analysis of observational data falls below that of individual clinical trials.

is no control group. An example of a case series would be a group of 20 women with ovarian cancer who had used talcum powder on their perineum prior to developing ovarian cancer. By their nature, case series are descriptive. They also generate hypotheses rather than testing hypotheses, and are not used to establish cause and effect. A major disadvantage of a case series is that this design generally suffers from selection bias. This means that the patients in the case series usually do not appropriately represent the wider population of patients. For example, a case series that reports on women with ovarian cancer who used talcum powder perineally likely does not represent the population of all women exposed to talcum powder and likely does not represent all women who developed ovarian cancer. Another issue with case series is that they lack a comparator group. Specifically, if the rates of perineal talcum powder use are similar between women who develop cancer (cases, who are in the series) and women who do not develop ovarian cancer (controls, who are not part of the series), there would be no evidence of an association or causal effect. However, since there are no controls in case series, it is not possible to make this comparison or identify an association between exposure and disease. Case reports and case series studies are not included in this report.

### 3.2 CASE-CONTROL STUDIES

A case-control study is an observational study that identifies two group of individuals: those with the outcome of interest (cases) and those without the outcome of interest (controls). The groups are compared to determine whether they differ with respect to an exposure of interest. These studies provide a higher level of evidence than case reports or case series because of the inclusion of a comparator group, the controls. An example of a case-control study is one where the cases are women with ovarian cancer and controls are women without ovarian cancer with the exposure of interest being perineal talcum powder use.

Well-conducted case-control studies use a pre-specified protocol that indicates how the cases and controls are to be identified and specifies how to measure the exposure. In theory, it should be possible for other investigators to use the protocol and obtain the same cases (with similar controls) and reproduce the values for the exposure of interest. Controls are often matched to cases on important aspects relevant to the outcome of interest. For example, since older women are more likely to develop ovarian cancer than younger women, a well-designed case-control study will select a control who is the same age as the case at the time she was diagnosed with ovarian cancer. The purpose of matching is to ensure that groups of cases and controls only differ with respect to the exposure of interest. For the question of perineal talcum powder use and ovarian cancer, the ideal case-control study would be one that matched controls to the cases with respect to all characteristics known to be associated with the risk of ovarian cancer, other than the exposure of interest (in this instance, perineal talcum powder use). If the groups of cases and controls appear similar on factors known to be associated with

ovarian cancer risk other than perineal talcum powder use, the association of perineal talcum powder use with ovarian cancer risk can be better isolated (unknown factors always remain a concern).

The advantage of a case-control study is that it can be accomplished in a relatively short period of time. Because the outcome status of the participants is already known at the start of the study, the participants do not need to be followed for a length of time to obtain a sufficient number of individuals with the outcome. All that needs to be collected or measured is the exposure of interest and potentially other variables relevant to the outcome of interest. A case-control design is a particularly attractive design for the study of outcomes that are relatively rare since it ensures that there will be a sufficient number of participants with the outcome, yielding adequate power. Power is the likelihood of detecting an association when there is an association to be detected. If a study has 80% power to detect a risk ratio of 1.3, this means that if the risk ratio is 1.3 or higher in reality, there is an 80% chance that the association will be statistically significant (i.e., it has a  $p\text{-value} \leq 0.05$ ). This is in contrast to a prospective cohort study (discussed next), which generally requires the recruitment of a large number of participants to ensure a sufficient number will develop the (relatively rare) outcome of interest. Both types of studies can be designed to have adequate power.

The major disadvantage of a case-control study is that it generally is not possible to ensure that the group of cases is similar to the group of controls on all aspects related to the outcome other than the exposure of interest. Most often, it is only possible to match cases to controls on two or three characteristics. Otherwise it becomes extremely difficult to find controls or becomes quite expensive in terms of having to obtain additional measurements of these variables on the participants. Many of the case-control studies that evaluate the association between perineal talcum powder use and ovarian cancer risk typically only match on a small subset of risk factors of ovarian cancer, e.g., age and location of residence. Examples of this include the Ness 2000<sup>3</sup> study (which frequency matched cases to controls by five-year age groups and three digit phone exchanges as a surrogate for residence), the Schildkraut 2016<sup>4</sup> study (which frequency matched controls to cases on residence and age), and the Cramer 2016<sup>5</sup> study (which frequency matched controls to cases by five-year age groups and region of residence). The inability to match the case group to the control group on all risk factors for ovarian cancer results in residual confounding. For example, suppose a case-control study matched cases to controls on the basis of age and location of their residence. The controls are likely to differ from the cases with respect to other important risk factors for ovarian cancer such as nulliparous status or BMI. If it is the case that obese women are more likely to apply talcum powder in the perineal region and that there is a greater proportion of obese women among the cases, then it cannot be ascertained whether any increased risk of ovarian cancer is attributable to obesity, perineal talcum powder use or both (or is unrelated). Obesity status and perineal talcum powder use

would thus be confounded in this example. There are statistical methods that can reduce the level of confounding, but they cannot eliminate it.

Case-control studies also suffer from biases inherent in the study design. One bias briefly mentioned above is *selection bias*. This occurs when cases and controls are selected in such a manner that they differ on important risk factors associated with the outcome other than the exposure of interest. To avoid such selection bias, the cases and controls would need to be similar with respect to all known risk factors associated with the outcome. This is difficult, if not impossible, to achieve in a case-control study. Sometimes it is just not possible to measure all the known risk factors, and even if it were, not all risk factors for ovarian cancer are known. Another common bias in case-control studies is *recall bias*. Recall bias occurs when cases and controls remember past exposures in a differential manner; e.g., cases might be more likely to remember an exposure than a control. If a woman knows she agreed to be in a study evaluating the association between ovarian cancer and perineal talcum powder use, for example, there is a likelihood that a case will recall perineal talcum powder use in greater proportions than controls, even if the usage rates between the groups is the same. Specifically, it has been documented that cases remember exposures to putative risk factors differently from controls<sup>6</sup> because of the desire to explain why they in particular got the disease. In studies of risk factors for breast cancer, women who have had the disease recalled a greater variety of risk factors they had been exposed to, including those falsely attributed to the disease in the media, such as use of oral contraceptives<sup>7</sup> and previous abortions.<sup>8</sup> This is a particular concern in the talcum powder literature because many of the case-control studies did not blind the women as to the purpose of the study, creating a risk of recall bias, in that the cases are more likely to recall potential putative risk factors, such as perineal talcum powder use, with a greater likelihood than controls. Recall bias of this type would generate an exaggerated association between perineal talcum powder use and ovarian cancer. If women with a disease become aware of a potential association between a risk factor and their disease, it would also increase the amount of recall bias. This is an even bigger concern for case-control studies conducted after lawyers began running advertisements regarding the prospect of litigation for women with ovarian cancer who used talcum powder products and after the publicity surrounding outcomes of court cases involving ovarian cancer and talcum powder use.<sup>4</sup> It should be noted that there is no statistical technique that can reduce or eliminate the effects of this bias.<sup>9</sup>

### 3.3 PROSPECTIVE COHORT STUDIES

Generally, in my experience, prospective cohort studies yield a higher level of evidence than case-control studies. A prospective cohort consists of a group of participants who differ with respect to certain factors under study and who are followed longitudinally over time. The goal is to determine how the factors of interest are associated with a certain outcome. A prospective

cohort study minimizes differential selection bias because cases and controls are selected prior to knowing the outcome of interest. Such studies also minimize recall bias because the exposure of interest is measured prior to the outcome, which limits the likelihood of differential recall between cases and controls.

A disadvantage of a cohort study is that the cohort needs to be quite large for outcomes that are relatively rare. The number of participants required for a cohort study is usually orders of magnitude larger than that for a case-control study. This substantially increases the resources needed to conduct the study since the exposures of interest and outcomes need to be measured on all the participants. Prospective cohort studies also require a longer time to conduct because the participants are followed longitudinally for outcomes that have not yet happened. Some outcomes of interest may require years to develop. Another potential disadvantage is that cohort studies are used to address multiple research questions, and this means that the exposure of interest may not be measured in the same way as it would if it were the only primary research question. However, this concern depends on the specific research questions of interest, and in general, it is an advantage to be able to measure exposure before the outcome is known.

There are several cohort studies evaluating the association of perineal talcum powder use and ovarian cancer.<sup>10-13</sup> All the cohort studies are large, with some having a sufficient number of women who were diagnosed with ovarian cancer to yield adequate power. Indirectly, this means that they have sufficient follow-up. First, many of the cohort studies recruited women who were 30 years or older: the Nurses' Health study recruited women in 1976 who were between the ages of 30-55 years, the Women's Health Initiative recruited women between 1993 and 1998 who were between the ages of 50 to 79 years, and the Sister Study recruited women between the ages of 35 to 74 years in 2003-2009. Because ovarian cancer is a disease of older women with a median age at diagnosis of 63 years, it would not require decades of follow-up to observe a sufficient number of cases. Second, it is reported that most women who use talcum powder started doing so when they were in their early adulthood.<sup>5</sup> Hence, there would be a sufficient time from time of exposure to allow for the development of ovarian cancer, if talcum powder use was a causal agent. One drawback of the cohort studies is that perineal talcum powder use was measured only at a single point in time, which raises the concern that women would be misclassified with respect to perineal talcum powder use if they started using it after they were asked about talcum powder use at the initiation of the cohort study. But the fraction of women who were misclassified because of this is likely quite low given that the mean duration of perineal talcum powder use in women that are ever-users is greater than 20 years, as reported in some case-control studies.<sup>14</sup> In addition, if women started after they were asked about use in the cohort study, the limited amount of follow-up time in the cohort studies would minimize the impact of misclassification under plaintiffs' experts' own

theories because they have taken the position that the lag time between exposure to talc and the alleged development of ovarian cancer from it is on the order of decades.<sup>15</sup> Finally, most of the prospective cohort studies did collect information on duration or frequency of use, which allows for an evaluation of dose-response.

Notably, most studies (both case-control and cohort) evaluated the perineal talcum powder exposure as ever versus never, even when they also investigated a dose-response relationship. This means it is possible to compare the observed association between ever versus never perineal talcum powder use between case-control studies and cohort studies. If there is a dose-response relationship, it should not depend on how the amount of exposure to perineal talcum powder is measured. It would be expected that if there is a dose-response relationship, it would be reflected as a higher likelihood of developing ovarian cancer cases with greater frequency of use, longer duration of use, or a larger cumulative number of doses. There is no evidence that the instruments used in the case-control studies to assess perineal/genital talcum powder exposure are more accurate than those used in the cohort studies.

### 3.4 RANDOMIZED CLINICAL TRIALS

Randomized clinical trials are considered a gold standard of evidence for a causal relationship because trial participants are randomly assigned to receive the treatment being evaluated or to receive the standard treatment (or placebo treatment if ethical). Randomization ensures that individuals who eventually develop the disease and those who do not are selected in the same way (i.e., it minimizes selection biases), similar to prospective cohort studies. However, the most important aspect is that it minimizes the chance that there are meaningful differences between the two groups with respect to risk factors for the outcome. It is the best method available to ensure that the two groups are similar on all risk factors other than the assigned treatment. This allows the researchers to isolate the treatment effect for the treated group when compared with the no treatment group because other variables are kept constant.

Generally, it is not feasible to perform a clinical trial to ascertain whether something is potentially harmful. Trials are conducted to evaluate the benefit of an intervention. Often times, potentially harmful effects of an intervention are observed in trials designed to evaluate the benefits of the intervention. These are recorded as adverse events, which essentially are unintended, detrimental effects. There have been no trials performed to determine the benefits of perineal talcum powder use. Hence, there are no randomized data that are relevant to assess potential adverse effects of perineal talcum powder use, such as the development of ovarian cancer.

Finally, meta-analyses of randomized clinical trials are sometimes considered to be the highest level of evidence, but this is not universally accepted.<sup>16-19</sup> Regardless, only meta-analyses of

randomized trials are purported to be the highest level of evidence and not meta-analyses of observational data (i.e., case-control studies or prospective cohort studies). The next section covers meta-analyses in more detail.

## 4 META-ANALYSIS

The term meta-analysis may encompass several distinct study designs. Designs relevant to this report are systematic reviews, pooled studies and meta-analyses.

### 4.1 SYSTEMATIC REVIEWS

A systematic review is a comprehensive, reproducible search for primary studies on a focused clinical question. High-quality systematic reviews are conducted according to a pre-specified protocol. The first step is to delineate a process for conducting a comprehensive search for relevant studies. Such a search yields a list of all studies that may potentially be relevant and generally is quite a large list. After all studies have been identified, they are reviewed and selected for inclusion in the systematic review according to transparent eligibility criteria that are contained in the protocol. Often times, the list of included studies is considerably smaller than the initial list because when reviewed for content, many studies are not relevant to the research question of interest or do not meet the pre-specified eligibility criteria. The purpose of a protocol is to ensure that a different set of researchers can use the protocol and arrive at the same set of studies.

Once all the studies have been identified, they are often assessed for quality, again using transparent and explicit criteria. Each study is then assigned a quality assessment, often a numerical value. The final step is to synthesize the information across the studies. This can be done in a qualitative fashion by summarizing in a narrative the information and quality of information contained in the studies and drawing conclusions based on this information. However, the information is often synthesized quantitatively to yield a single estimate of an effect size or the strength of an association, such as between perineal talcum powder use and ovarian cancer risk. The mathematical process that combines the results is essentially a weighted average of the results in the individual studies using the quality score, study sample size, or some combination as the weights. The process of quantitatively combining the results is called a meta-analysis.

### 4.2 POOLED STUDIES

Individual participant data studies, often called pooled studies, are those that use participant level data from published, and sometimes unpublished, studies. This is in contrast to meta-analyses that only combine the summary values that are available within the published

manuscript; a meta-analysis does not have access to the patient values that yielded the summary values. An advantage of a pooled study is that it can better adjust results for confounding variables than can be done in a meta-analysis. For example, suppose there are two studies, one of which reports an association (say an odds ratio) adjusted for the age and nulliparous status of the woman, and the other of which reports an adjusted odds ratio for age and place of residence of the woman. A meta-analysis would average these two adjusted risk ratios even though they are adjusting for different sets of variables. On the other hand, a pooled study would have access to the individual participant data of these two studies and – if both studies collected information on age, nulliparous status, and residence for each woman – would allow the researcher to compute an adjusted risk ratio that appropriately adjusts for all three factors.

Another advantage of a pooled study over a meta-analysis is that it is often possible to perform different subgroup analyses that are not feasible in a meta-analysis. For example, a meta-analysis might provide results of perineal talcum powder use according to different applications such as dusting of sanitary napkins, dusting of underwear, or direct application to the perineum, but it might be that not every individual study provides results for the different types of applications. If the individual patient level data were available to the researcher and both studies did record the type of perineal application, the researcher could compute the associations for each type of application across the pooled studies. In the studies considered in this report, there was a single pooled study, by Terry et al.<sup>20</sup>

#### 4.3 META-ANALYSIS

The purpose and some of the capabilities and limitations of meta-analyses have already been alluded to in the preceding sections. In summary, a meta-analysis attempts to evaluate the effect of an exposure by combining the effects reported in published studies. Unlike pooled studies, meta-analyses are not premised on individual patient data, and instead rely on the summary values reported in the publications. Nevertheless, meta-analyses of the same underlying studies can produce widely varying results depending on a range of factors, including, in particular, the studies that are included and how to weigh them.

In theory, a well-designed meta-analysis that draws from a robust pool of individual studies should provide high-quality evidence concerning an association. Indeed, as mentioned above, some have proposed that meta-analyses of randomized clinical trial data are the highest level of evidence. But there is disagreement on that point and research that illustrates some of the limitations of meta-analyses. For example, there have been several studies conducted that compared the results of a meta-analysis of several small randomized trials and a subsequent large randomized trial.<sup>21</sup> Those studies found that the meta-analysis results would have led to the adoption of an ineffective treatment in 32% of the cases or led to the rejection of a useful

treatment in 33% of the cases. Publication bias would lead to a false positive result, meaning the meta-analysis indicated the treatment was effective (i.e., statistically significant difference) and the subsequent randomized trial did not detect a difference in effectiveness between the treatments. Publication bias arises from the tendency for investigators to preferentially submit studies with statistically significant results, and for editors to accept them. Although it is possible to test for publication bias, these tests are often underpowered.

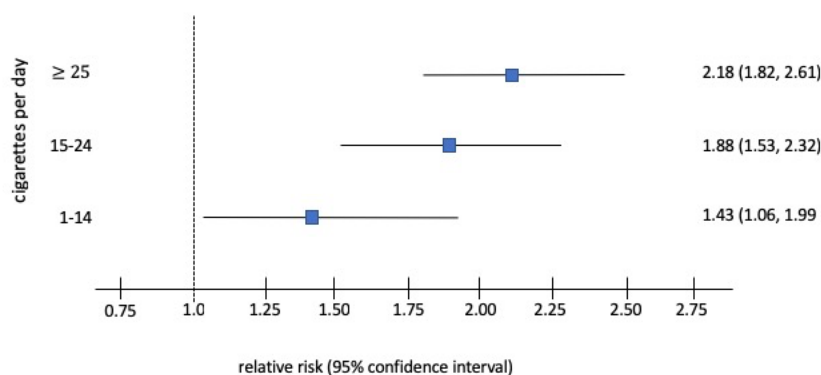
Another potential problem with meta-analyses is that the results of meta-analyses are considerably influenced by subjective choices made by the authors.<sup>22</sup> Specifically, when investigators perform a meta-analysis, they make decisions regarding (1) the primary studies that are included, (2) the effect measures that will be used (e.g., relative risk of the outcome, difference in the proportion of patients with the outcome, etc.), (3) the choice of the quality assessment scale, and (4) the choice of the averaging technique that will be used to combine the summary values across the studies. Different investigators may make different choices, which would lead to different estimates. Of considerable concern is determining whether studies are similar enough to be included in a meta-analysis. Often investigators choose to only include a very narrow range of studies, such as only clinical trials or only case-control studies, because other types of studies yield differing results. This is problematic because it is instructive to understand what the differences imply, which may often be the consequence of biases inherent in different types of study design. Specifically, it may be the case that the analysis is not meaningful if there is discordance between the results of different study types, such as case-control studies and cohort studies. This has led researchers to advocate more reliance on the Hill criteria (discussed further below) and less deference to meta-analysis. As one article explained, “meta-analyses ought not be considered the best kind of evidence for assessing causal hypotheses in medicine” because they rely on a narrow range of evidentiary diversity.<sup>22</sup> By contrast, Hill’s framework should be employed, since it considers all evidence available (case-control studies, cohort studies, randomized trials, animal studies, cell line studies, etc.).

Finally, meta-analyses are particularly suspect when they combine observational data, as opposed to randomized trial data. This is so because “[d]ue to the effects of confounding and bias, such observational studies may produce estimates that deviate from the true causal effects beyond what can be attributed to chance.”<sup>23</sup> “Combining a set of epidemiological studies will thus often produce spuriously precise, but biased, estimates of association.”<sup>23</sup> Confounding and differential measurement error are serious problems in studies of exposures that are linked to lifestyle. When Ioannidis et al.<sup>24</sup> compared the results of randomized versus non-randomized studies, they found that discrepancies beyond chance were observed. Specifically, the differences observed between the randomized studies and non-randomized studies were found to be statistically significant in 16% of the studies. The study also found that differences in estimated magnitude of associations are common, with 33% of the studies having

a two-fold difference between the randomized trials estimate and non-randomized studies estimate of the odds ratio, and 62% having a 50% difference in the odds ratio.

The concerns about biases in observational studies and meta-analyses of observational studies are not just theoretical. A meta-analysis of four prospective studies of middle-aged men explored smoking as a risk factor of suicide.<sup>16</sup> All the cohort studies showed a positive association between smoking and suicide. A meta-analysis of the cohort studies based on approximately 390,000 men demonstrated a dose-response relationship, with increasing number of cigarettes smoked per day associated with increased risk of suicide (Figure 2). It would be tempting to conclude that the association is causal due to the demonstrated dose-response relationship in the meta-analysis and consistency of the risk ratios of the association across the cohort studies, if there would have been a plausible explanation (but there is none).<sup>25</sup> Instead, the observed association is likely due to confounding of risk factors for suicide and smoking status, such as the fact that individuals with increased anxiety are more likely to commit suicide and are more likely to smoke.

FIGURE 2: ASSOCIATION BETWEEN NUMBER OF CIGARETTES AND SUICIDE



One of the most important biases that exists in case-control studies relative to cohort studies is *recall bias*. For example, a comprehensive meta-analysis showed an association between higher intake of saturated fat and risk of breast cancer.<sup>26</sup> However, while a meta-analysis of the 12 **case-control** studies showed a statistically significant association between increased intake of saturated fat and increased breast cancer risk (risk ratio of 1.36), there was no association observed in a meta-analysis of six **cohort** studies (non-significant risk ratio of 0.95). The discrepancy between the case-control studies and cohort studies is likely due to recall bias from the dietary items and selection of the study participants, yielding a spurious association in the case-control studies.<sup>27</sup> Simply put: women with breast cancer are more likely to remember engaging in potentially unhealthy activities like eating saturated fat.

Since all the meta-analyses for evaluating the purported association between use of perineal talcum powder and ovarian cancer are based on observational studies, the large majority of which are case-control studies, caution must be employed in drawing conclusions from those meta-analyses since “...even if adjustments for confounding factors have been made in the analysis, residual confounding remains a potentially serious problem in observational research.”<sup>16</sup> In addition, when there are differences in the magnitude of an association between case-control studies and cohort studies, it does not make sense to combine them in a single summary. As discussed above, case-control studies have more biases than cohort studies. If there are a greater number of individuals in case-control studies than cohort studies, the result of combining all studies will naturally reflect the associations seen in the case-control studies due to their larger sample sizes. Hence, this will mask the difference in results between the lower level of evidence case-control studies and the higher level of evidence cohort studies. When there are differences in terms of magnitude of associations and statistical significance of associations between case-control studies and cohort studies, the meta-analysis should be stratified by the study type, with a case-control study meta-analysis summary and a cohort meta-analysis summary. As stated by Feinstein,<sup>19</sup> “[w]ith meta-analytic aggregates, however, the important inconsistencies are ignored and buried in the statistical agglomeration.” This is especially true if there are considerably more studies of one type, as is the case here.

Although implausibility of results can sometimes protect against reaching misleading claims, it is surprisingly easy to produce reasonable explanations for causality even when causality is absent. In studies of the association of beta carotene and risk reduction of cardiovascular disease and cancer, a plausible hypothesis is that beta carotene has antioxidant properties and therefore prevents carcinogenesis and atherogenesis by reducing oxidative damage to DNA and lipoproteins.<sup>28</sup> This hypothesis was consistent with the results of a meta-analysis of observational studies that found a statistically significant reduction in cardiovascular deaths between individuals in the high beta carotene group compared to those in the low beta carotene group. However, a meta-analysis of clinical trials randomizing participants to beta carotene supplements versus no supplements found a statistically significant 12% increase for cardiovascular death. Similar discrepancies between the analysis of the observational studies and randomized trial data were observed for the cancer outcome.<sup>16</sup> The subsequent conclusion was that there is no evidence of beneficial effects of beta carotene supplements in terms of reduction in cardiovascular disease and cancer incidence.

## 5 APPROACH

The main focus of this report is whether perineal exposure to talcum powder causes ovarian cancer. As mentioned previously, the gold standard for answering that question would be a randomized trial that would randomly assign women to a group that would apply talcum

powder to the perineum after bathing or to a group that would apply some other powder (say cornstarch) to the perineum after bathing. Ideally, the women and investigators would not know the group to which a participant was assigned. The women would then be followed over a long period of time and assessed for ovarian cancer. Such a trial would not be feasible, however, for several reasons. The first is that if it is felt by some that perineal talcum powder use causes ovarian cancer, it would not be ethical for them to enroll in the trial. Even beyond that, given the fact that ovarian cancer incidence is so low, it would not be feasible to conduct this trial in terms of the number of patients (thousands) that would need to be recruited and the length of follow-up that would be needed. The trial would need to enroll women with no exposure to perineal talcum powder and then randomize them between continue not to use or to start use. It could potentially be difficult to find women with no exposure if the true exposure rate is as high as 50%, as reported by some studies and knowing that less than 3-5% of eligible people choose to participate in a clinical trial. The length of treatment would likely need to be quite long, which means there would be issues of non-compliance. Finally, by the time the trial were completed with the requisite number of observed ovarian cancer cases, it would be decades later and the question would probably no longer be of interest. In addition, there are no randomized data regarding the development of ovarian cancer as an adverse event associated with perineal talcum powder use. To date and for the foreseeable future, the only available human data with respect to the evaluation of an association between perineal talcum powder use and ovarian cancer are from observational data: case-control studies and cohort studies.

As between these two types of observational data, the level of evidence for establishing causality is greater for prospective cohort studies (see Figure 1). As indicated, prospective cohort studies minimize biases such as recall bias and participant selection bias, which is why they have a higher level of evidence than case-control studies. Based on my experience, there needs to be overwhelming and compelling evidence to overcome the scientific consensus and conclude that case-control studies offer a higher level of evidence. Absent such compelling circumstances, if there is a conflict in results between prospective cohort studies and case-control studies, it is scientifically justified to place more weight on the results from the prospective cohort studies, since they have fewer biases than case-control studies.<sup>29</sup>

## 5.1 BRADFORD HILL FRAMEWORK

The framework I use for evaluating the evidence of whether perineal talcum powder exposure causes ovarian cancer is that proposed by Bradford Hill.<sup>1</sup> The framework is meant to be applied to all available, relevant data, including cell line data and animal data, as well as human data. The more aspects of the framework that are met, the greater the likelihood of a causal relationship. There is a greater certainty of a causal relationship between an exposure and

outcome when more of the evaluated criteria are met. In addition, the strength of the observed association between exposure and the outcome influences how demanding the remaining criteria in the framework are in evaluating whether a causal relationship exists. Specifically, if the human data consists primarily of observational data and the observed association is small to modest (say a risk ratio less than 2.0), there needs to be more compelling evidence on the other Bradford Hill factors to support a causal relationship because it is known that residual confounding is more likely to yield small to modest associations than is causality. Hence, observational studies that yield small to modest levels of association require a higher level of supporting evidence to reach a conclusion of causality than do studies with strong levels of association.<sup>30,31</sup>

#### 5.1.1 STRENGTH OF ASSOCIATION

This criterion evaluates the strength of the relationship between the exposure and the outcome. Hill explained that “the larger an association between exposure and disease, the more likely it is to be causal.”<sup>32</sup> A classic example is the investigation of scrotal cancer incidence in chimney sweeps. The rate of scrotal cancer was nearly 200 times greater in chimney sweeps than in other occupations.<sup>32</sup> This ultimately led to a determination that chimney soot likely causes scrotal cancer. On the other hand, Hill suggested that small associations are less likely to be causal because they could more conceivably arise from other factors, such as bias and confounding. In fact, there have been such examples, like the observed, statistically significant, associations between smoking (the exposure) and suicide (the outcome) cited earlier that was not found to be causal.

Today, researchers have the ability to collect much larger datasets and have access to a greater number of publications, which leads to quite small associations being statistically significant. As such, statistically significant results are not always biologically meaningful or methodologically appropriate for inferring causality. If the small association arises from observational data, rather than randomized data, further evidence is required to demonstrate that this is not merely a spurious result arising from confounding or biases. This is not to say that small associations are never indicative of a causal relationship, but rather that they require a thorough examination of the underlying study design, “comparison to the weight of evidence in the literature, and consideration of other contextual factors, including the other criteria” listed below.<sup>32</sup>

In terms of applying this criterion, it is meant to be the association between exposure of interest and the outcomes. Specifically, a relative risk of 1.2 to 1.3, which is what is reported in most of the meta-analyses I reviewed, is a relatively weak association. This is true regardless of how serious or prevalent the outcome of interest may be. Contrary to the suggestions of several of plaintiffs’ experts, the ultimate impact that a relative risk may have on public health

is not relevant for the ascertainment of this criterion. Specifically, to determine the impact on public health, one needs to assume that the association is causative. If it is not causative and only the consequence of confounding, removing the exposure would not reduce the outcome because it is not causative. For this reason, it is circular reasoning to measure the strength of the association in terms of its potential to be causal based on the impact on public health.

#### 5.1.2 CONSISTENCY

This factor requires that multiple studies across different locations, populations, and study designs show a similar association between the exposure and the outcome.<sup>1</sup> Results across studies are consistent if the risk ratios are numerically close to one another and the results are statistically significant in most studies. Note that it is not necessary that all studies have statistically significant results since the p-value, which is a measure of the likelihood that results occurred due to chance, is considerably influenced by the sample size. Smaller studies have less power, meaning that even if a smaller study has the same risk ratio as a larger study, the p-value of the smaller study may be larger than 0.05, or non-significant. However, if adequately powered studies do not achieve statistical significance, this is evidence of inconsistency. Another way inconsistency can arise is if the 95% confidence intervals for the risk ratio estimates have no to little overlap with one another. For adequately powered studies, if one study has a statistically significant result and the other does not, it means that the magnitude of the relative risk differs considerably, which is an inconsistency between the size of the estimated relative risks.

When evaluating observational data, it is also important to have similar results across the different study designs; that is, the results for case-control studies and cohort studies should be numerically similar and statistically significant if adequately powered. In the situation where the case-control studies are generally consistent but differ from results of the cohort studies, which are generally similar to each other, this criterion is not met. If an association is truly causal, it would be observed regardless of the type of study design. When the results across study designs are not consistent, i.e., case-control studies report a statistically significant association and cohort studies do not, the study with the accepted higher level of evidence is the cohort study because it eliminates biases such as recall bias.

#### 5.1.3 SPECIFICITY

When this was proposed, it meant that associations are more likely to be causal when the exposure causes only one disease. This criterion was proposed in an era when exposure was often defined in terms of proxies for the true (often unknown) factor. Examples are occupation (e.g., chimney sweep) or residential location. Today, exposures are defined at a much finer level, such as the dose of a specific chemical. Oftentimes, the exposure being evaluated can be associated with numerous diseases or a disease arises as a result of a number of different

exposures, or even a mix of exposures. While there are examples of highly specific exposure-disease associations, the original criterion of specificity is widely considered weak or irrelevant in modern epidemiology.<sup>32</sup>

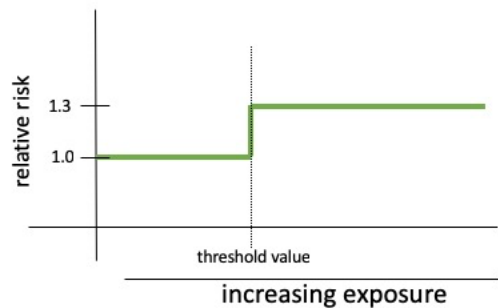
#### 5.1.4 TEMPORALITY

For an association of an exposure to a disease to be causal, the exposure must precede the onset of the disease. There is universal agreement among epidemiologists that this criterion must be met for an exposure to cause a disease. Sometimes it is difficult to ascertain whether this criterion has been met if the disease and exposure are measured in close proximity of one another. For example, suppose it is suspected that a drug causes a cancer and that an individual was prescribed the drug six months before their cancer was diagnosed. In this example, it is unlikely that the drug caused the cancer, although the individual did start taking it prior to being diagnosed, because cancer tends to have long latency periods. Due to the healthcare interaction, the individual likely may have undergone additional examinations at the time they were prescribed the drug or during follow-up for the treatment that led to discovery of the pre-existing cancer. Therefore, even though exposure preceded the diagnosis, it is unlikely that the drug exposure caused the disease; instead, it is likely that the exposure only preceded the diagnosis of cancer, not the cancer itself. This can be labeled as temporal ambiguity or detection bias.

#### 5.1.5 BIOLOGICAL GRADIENT

A biological gradient – or dose response – is present where the risk observed depends on the degree of exposure. Hill stated that “if a dose response is seen, it is more likely that the association is causal.” In particular, the demonstration of a dose-response relationship provides clear evidence of a causal relationship. The most commonly assumed relationship is monotonic, which means that increasing doses are associated with increasing risks. However, there are more complex dose-response relationships, such as a threshold model. In that model, the disease risk only increases once the exposure hits a specific level and then remains constant for further increases in dose (Figure 3).

FIGURE 3: EXAMPLE OF A THRESHOLD DOSE-RESPONSE RELATIONSHIP



Regardless of the nature of the dose-response relationship, it needs to be demonstrated consistently across the available studies. Specifically, the same type of dose-response relationship needs to be exhibited in the different studies. If a threshold relationship is hypothesized, it would require evidence of the threshold value as well, and the value is similar across the studies. If only a few studies exhibit a dose-response rather than all, this criterion would not be convincingly met.

#### 5.1.6 PLAUSIBILITY

This criterion is satisfied if the observed association is consistent with the available information and knowledge regarding the etiology and mechanism of disease. The state of knowledge of disease mechanisms and the tools available to researchers today are considerably more sophisticated and advanced compared to the era in which Hill proposed this criterion. They allow researchers to posit and test more aspects of the exposure-to-disease pathway. As such, this criterion plays a greater role in establishing causality than in previous decades and will continue to grow in importance as scientific advances continue to be made. Specifically, researchers are better able to predict plausible relationships using in vitro and in vivo models that isolate defined disease mechanisms, which represents a paradigm shift in how evidence for causality is obtained.<sup>32</sup> Plausibility requires support from biological or mechanistic studies. It cannot just be something that sounds reasonable. Without supportive biological data, the criterion is not satisfied.

#### 5.1.7 COHERENCE

Hill proposed that there should be coherence between epidemiology and laboratory findings. An example of this would be that if a dose-response relationship is proposed, based on the epidemiology studies, it is not contradicted by evidence arising from cell line and/or animal studies.

This criterion is closely related to biological plausibility in that the evidence of a causal effect of an exposure should make logical sense based on all the available information, consistent with biological plausibility evidence. Specifically, evidence for a causal association requires coherence across all the available data; e.g., cell line, animal and human data. If there are contradictions among the available information, it cannot be concluded with reasonable scientific certainty that the association between the exposure and disease is causal.

#### 5.1.8 EXPERIMENT

Hill stated: “Occasionally it is possible to appeal to experimental evidence.” In this context, he primarily meant randomized trials in humans. As discussed, there are no randomized data available regarding perineal talcum powder exposure and ovarian cancer, and likely such data will not become available in the future. Hill also explained that in addition to randomized trials that assign individuals to the exposure or not, another set of evidence would be that disease risk declines following the cessation of an exposure. Although such an experiment might be feasible for perineal talcum powder use and ovarian cancer, it may not result in observable decreases in ovarian cancer incidence. It is likely that ovarian cancer follows a complex development pathway and cessation of perineal talcum powder exposure (even if such exposure is posited to be a cause of cancer) may not reverse or appreciably slow the progression toward the development of ovarian cancer.

#### 5.1.9 ANALOGY

This criterion essentially means that when there is strong evidence of a causal association between a particular exposure and a specific disease, investigators should be willing to accept weaker evidence when evaluating whether a similar exposure causes a similar disease. One example where this criterion was successfully satisfied is with respect to the health risks of second-hand cigarette smoking. There is considerable similarity between primary and secondary cigarette smoke exposure and the subsequent disease that develops after exposure is the same. Hence, the level of evidence for causality was lower for second-hand smoke than for establishing a causal relationship between primary cigarette smoking and various diseases, including a smaller strength of the association.

While lack of analogy does not preclude causation, invoking it does not necessarily support causation, especially because a substantial body of knowledge exists to identify an analogy for almost every situation.

### 5.2 APPROACH FOR FORMING MY OPINION

My opinion is based on a review of all the relevant epidemiology literature relevant to evaluating the association between perineal talcum powder use and ovarian cancer. I considered case-control studies, prospective cohort studies, and meta-analyses; I did not find

any data arising from randomized trials of talcum powder. I did not read or evaluate case reports or case series given the low strength of evidence provided by such studies. Since all the epidemiology studies are observational, I carefully considered the amount of evidence there is for biases and residual confounding that may be affecting study results.

Biases and residual confounding are inherent in observational study designs to varying degrees. The starting premise is that these are the most logical explanations for the observed association and in order to conclude with reasonable scientific certainty that the association is causal, there must be evidence that these biases and residual confounding are minimal. In other words, if there is evidence of residual confounding and biases, the epidemiology studies would not allow one to conclude with scientific certainty that the association is causal.<sup>30</sup> It is worth mentioning that it is not appropriate to expect an observational study to prove there is not a causal relationship. The starting scientific premise is that there is no causal association, and it must be proved that there is one.

Since all the epidemiologic evidence at issue here is observational (versus having randomized data) with either no or weak associations, any causal assessment must generally be more demanding, requiring a greater number of Hill criteria to be met, with more convincing evidence.<sup>30</sup> As mentioned by many of plaintiffs' retained experts, it is not required that each criterion be met. Rather, the criteria provide a framework for integrating and interpreting data across all existing evidence arising from cell line, animal, translational and human studies. My primary expertise lies in the critical appraisal of the conclusions that can be drawn based on data contained within and across human studies. I focus on the evidence in the epidemiologic data versus the mechanistic and laboratory data. However, the relatively weak evidence for a casual association that can be obtained from the observational epidemiologic data demands stronger evidence in the cell line, animal and translational studies for how perineal talcum powder exposure leads to ovarian cancer. There needs to be convincing mechanistic data that support the components implied by the biological plausibility hypotheses that have been put forward. These data need to meet the coherence criterion described above in order to reach the conclusion of causality with scientific certainty.

In my evaluation of the epidemiology data, I primarily assess the degree to which the criteria of strength of association, consistency of the association, temporality, and biologic gradient have been met. If the strength of the association is weak or modest (say a risk ratio under 2), epidemiologists require more of the additional criteria to be met in order to reasonably rule out a spurious association that is a consequence of the inherent biases and residual confounding in the observational studies.

In the remainder of the report, I (1) review the information available at the time of the 2010 IARC report, (2) review subsequent information that has become available since the report and

whether it does or does not differ from the previous data, (3) assess the opinions rendered by some of plaintiffs' experts, and (4) offer my opinion based on my analysis of all the information I reviewed.

## 6 REVIEW OF THE EPIDEMIOLOGY DATA

For my review, I started with the seven meta-analyses<sup>33-39</sup> and the one pooled study<sup>20</sup> to identify the initial set of studies published that were relevant to perineal/genital talcum powder exposure and its potential association with the development of ovarian cancer. In particular, I was interested in any study that involved a form of genital/perineal talcum powder exposure, including application to the perineal, genital, or rectal area and/or use on sanitary pads, diaphragms, underwear, tampons, or condoms. There were varying definitions across the different studies with respect to genital/perineal exposures identified. One meta-analysis only pertained to talcum powder application to diaphragms.<sup>40</sup> Next, I undertook my own search of the literature to identify whether there were additional studies that were not contained within the meta-analyses or pooled study relevant to perineal talcum powder exposure and ovarian cancer. I did not identify any additional studies. My review was of 30<sup>5</sup> case-control studies<sup>3,4,14,33,35,41-64</sup>, three cohort studies<sup>10-13,65</sup> (comprising five publications because one was an update to the Nurses' Health Study cohort<sup>12</sup> and the other analyzed a subset of women in the Nurses' Health Study<sup>65</sup>), one pooled analysis,<sup>20</sup> and seven meta-analyses.<sup>33-39</sup> Subsequently, I was provided a draft of another meta-analysis conducted by Taher et al.<sup>66</sup> that has not yet been published. In addition, I reviewed the IARC report.<sup>2</sup> I am confident that my review is comprehensive and contains the highest-quality studies published in the highest-impact journals. If there are any studies I did not find, they would be of lower quality and likely with relatively small sample sizes and therefore it is unlikely that any such study would alter my opinion.

### 6.1.1 STRENGTH OF ASSOCIATION

This criterion does not have a hard threshold. There is no cut-off value for the magnitude of an association between an exposure required for the relationship to be causal. However, it is the case that larger magnitudes of association in observational studies are more likely to reflect a causal relationship, whereas smaller associations are likely to reflect biases and confounding inherent in the observational study designs. Most epidemiologists regard relative risks (either odds ratios or risk ratios) that are less than 1.5 to be weak relationships.<sup>1,32,67,68</sup> Although there are instances in which ratios under 1.5 are established to be causal based only on observational data, there are more instances where they are spurious due to confounding or biases.<sup>67</sup> When relative risks of an association are relatively small, it is necessary to rule out residual confounding and biases, making the role of other criteria more important.

The reported association (odds ratio) between perineal/genital talcum powder exposure and ovarian cancer across the case-control studies ranges from approximately 0.92 to 1.97. (The upper value is statistically significantly greater than 1.0; there are some higher non-significant values that have been reported.) The reported association (relative risk) across cohort studies ranged from approximately 0.73 to 1.12 and none of these associations is statistically significantly different from 1. There was one pooled analysis<sup>20</sup> and it reported a modest statistically significant association of 1.24. The meta-analyses all report statistically significant associations between approximately 1.22 to 1.35. The exposure definitions differed across the studies from ever/never to regular use, which was also defined differently across studies.

While it is true that weak associations may arise if an exposure is a causal agent of an outcome if other Hill criteria are satisfied, the ultimate public health impact does not provide evidence of whether the exposure is causal or not. One plaintiffs' expert<sup>15</sup> has indicated that there have been instances in which public health recommendations were based on observations of weak associations. However, the mere fact that precautionary recommendations are made is not evidence that the associations are causal. Many of the examples cited by plaintiffs' experts have not been demonstrated with reasonable certainty to be causal, such as alcohol and risk of post-menopausal breast cancer or air pollution and cardiovascular disease. In other examples cited, the recommendations were based on data from randomized trials, which essentially are free of residual confounding and yield the strongest evidence of a causal relationship: e.g., estrogen-progestin menopausal hormone therapy (HT) and breast cancer risk, and the prevention of skin cancer through the use of sunscreen. For clinical trial data, the residual risk has been minimized by randomizing patients to treatment and control groups. Hence, there is a high likelihood that any significant association that is observed is due to the assigned treatment (or exposure); there is little concern regarding a spurious result due to bias or confounding, and so the size of the association is not an issue. Thus, the association between sunscreen and reduced skin cancer risk, for example, has been established as causal despite relatively small associations because of data from randomized trials and not because recommendations have been made on the basis of the association. Another plaintiffs' expert cites similar examples of small associations that are deemed causal and concludes that there is similar evidence for talcum powder and ovarian cancer as there is for passive smoke exposure and lung cancer.<sup>69</sup> It is correct to conclude that the associations are of similar magnitude, but incorrect to conclude because one is accepted as causal, so should the other based solely on the similar size of the associations. The mere fact that there have been weak associations established as causal does not furnish a sufficient basis for concluding that perineal/genital exposure to talcum powder causes ovarian cancer.

Another plaintiffs' expert states that the association between perineal talcum powder use and ovarian cancer is strong because of the public health impact overall.<sup>69,70</sup> Specifically, Dr. Smith-

Bindman concludes that because a very large number of ovarian cancers are purportedly caused by talcum powder, and talcum powder use provides no medical benefit, the Hill criterion of strength of association is important and met. However, these statements employ circular reasoning because they assume that the relationship between talcum powder and ovarian cancer is causal, when ascertaining causality is the entire purpose of the Bradford Hill inquiry. Only if the association were causal would there be a considerable public health impact; therefore, the possibility that there could be a considerable health impact if causation were proven is not evidence that the association between the exposure and subsequent development of disease is strong. Determining the strength of the relationship between an exposure and a disease is not made on the basis of the potential public health impact.

Smith-Bindman also misinterprets why the strength of an association is important. She states that although a larger association between exposure and disease may be easier to identify, this does not mean that it is more likely to indicate causality or importance. That is not correct. As I describe above, the issue with the strength of an association in observational studies is that smaller associations are more likely to arise from inherent confounding and biases in the study design. It is not that smaller associations are harder to detect and therefore less likely to be causal.

Another plaintiffs' expert argues that in a rare disease such as ovarian cancer, it is not uncommon to observe relatively small associations that are causal.<sup>71</sup> This is not true. The prevalence of the disease does not impact the strength of an association. Even for rare diseases, an association of 1.3 or less is still considered small and with a large likelihood of being spurious, without considerable supporting evidence to the contrary. The level of evidence for causality is not relaxed in instances of rare diseases, even in the case of deadly diseases such as ovarian cancer.

It is my opinion that the association between perineal/genital talcum powder exposure and ovarian cancer is about 1.3, based on the case-control studies, and that there is no statistically significant association demonstrated in the cohort studies. This means it is a relatively weak association that is likely to be spurious, arising from residual confounding or inherent biases. As such, this increases the importance of other criteria in the Hill framework for establishing that the relationship is causal.

#### 6.1.2 CONSISTENCY OF RESULTS

Given the relatively weak association between perineal/genital talcum powder exposure and ovarian cancer as reported in some of the case-control studies, this criterion is quite important. Specifically, if there is a lack of inherent confounding and biases in the observational studies, the results across the different study designs should be consistent if the relationship is causal. There are three different designs of the primary studies: case-control using population controls,

case-control using hospital controls and prospective cohort studies. Consistency among meta-analysis data is not as informative since the meta-analyses synthesize subsets of the same studies. Obviously, more recent meta-analyses will contain more studies than earlier one because more studies have been published in the intervening time. Typically, more recent meta-analyses essentially incorporate all the studies contained in earlier meta-analyses and add studies published subsequently. Since meta-analyses encompass essentially the same set of studies (if performed about the same time) or subsets of studies contained in more recent meta-analyses, it would be expected that they yield similar results.

There is considerable variability among the estimates of the association between perineal/genital talcum powder exposure and ovarian cancer for the case-control studies. As mentioned above, the results for case-control studies range from 0.92 up to 1.97, which was statistically significant. Looking across all the results of all the case-control studies, the range is from 0.92 to 3.90, where 3.90 was not statistically significant. Clearly the results are not consistent in terms of the reported magnitude of association across the case-control studies. The largest reported association is almost 4 times greater than the smallest reported association. One issue is that the not all results were statistically significant, but this could be driven by sample size. On the other hand, the results across the cohort studies for the association between perineal/genital talcum exposure and ovarian cancer are consistent in that none of the results is statistically significant for the different cohorts: Nurses' Health Study, Women's Health Initiative, and the Sister Study. The magnitudes of the relative risks were also relatively consistent rating from 0.73 to 1.12; the largest is about 1.5 times greater than the smallest.

A possible explanation for the wide range of associations within the case-control studies is the use of different control populations. In selecting a control population, the ideal is to match the cases on all risk factors for the outcome of interest other than the exposure being investigated. For this study, it would mean selecting a control group that is similar to the case group with respect to established ovarian cancer risk factors such as age, nulliparity status, germline mutational status (e.g., BRCA1/2), and family history of ovarian cancer. Matching to such a degree is typically not possible in a case-control study. And in fact, most talcum powder case-control studies only matched for age and perhaps geographic residence of the case. An obvious difference between population controls and hospital controls is that the population controls are generally healthier than hospital controls. However, if there truly were a causal relationship, it would be expected to be seen in different control groups unless there is compelling evidence that a control group is biased toward having women with more ovarian cancer risk factors than the cases. The range of values for case-control studies with hospital controls was 1.13 to 1.70, and none of the results was statistically significant. This range is considerably smaller than what

is seen in studies with population-based controls. At the very least, this suggests that the wide range is not due to the inclusion of hospital-based controls.

The larger inconsistency is between the case-control studies and cohort studies. It is well established (as discussed above) that there is more potential for confounding in case-control studies compared to prospective cohort studies since prospective cohort studies are not prone to participant selection bias and recall bias with respect to the exposure, which is why they are considered to yield a stronger level of evidence than case-control studies. And here, not only were the magnitude of the associations meaningfully different, the association was not found to be statistically significant in the cohort studies. Specifically, according to two recent meta-analyses,<sup>38,39</sup> the estimates of the association of ever exposure of talcum powder to the perineal/genital region versus never use for the case-control studies was 1.26 (95% CI: 1.17 to 1.35) and 1.35 (95% CI: 1.27 to 1.43) compared to 1.02 (95% CI: 0.85 to 1.20) and 1.06 (95% CI: 0.90 to 1.25) for cohort studies. This divergence is all the more striking in light of the fact that the lack of statistical significance in the meta-analyses of the prospective cohort studies is not due to lack of power. Across the three different prospective cohort studies, there were approximately 1,400 women diagnosed with ovarian cancer and more than 200,000 women who were not diagnosed with ovarian cancer. This is in the range that Narod<sup>72</sup> proposes is needed to have sufficient power in a cohort study, although he does not provide a power calculation to support this number. The power to detect a hazard ratio of 1.20 or larger is over 90%, with a two-sided level of significance of 0.05. Clearly, there is sufficient power for an association of 1.26, that observed in the case-control studies, to be found statistically significant. This means that it is very likely that the true association within cohort studies (if any) is less than 1.20. In fact, the Berge et al.<sup>38</sup> study found that there was a statistically significantly different association for the perineal/genital talcum powder exposure and ovarian cancer between the case-control studies and cohort studies (p-value = 0.007). There is a clear inconsistency between the different study types, with case-control studies yielding a statistically significant association ranging from 1.26 and 1.35, and cohort studies yielding a non-significant association ranging from 1.02 to 1.06. Hence, there is no evidence of a causal relationship because the results are inconsistent.

Arguments have been made by all of plaintiffs' experts that the results are consistent. Some experts emphasize what they see as the relative stability of the estimates across time, in diverse populations and across diverse study designs.<sup>70,71</sup> Unfortunately, they do not indicate what is meant by relative stability. A range of the smallest association to the largest being four times different is not an indication of stability of the magnitude of association. Furthermore, there was a considerable difference in strength of the association yielded by case-control studies and cohort studies. Other plaintiffs' experts say the results are consistent because they consistently produced a risk ratio  $> 1$ <sup>73,74</sup> or  $> 1.1$ .<sup>15</sup> This is quite a broad metric because the

results that cover a range of 100-fold from smallest observed value to largest observed value would meet this criterion. Furthermore, plaintiffs' expert Dr. Siemiatycki argues that if there was no causal relationship, one would expect to see as many risk ratios lower than one as there are higher than one. This would only be true if there were no residual confounding or biases within studies, which is not true for observational studies. In particular, if there were clinical trial data, it then would be expected that roughly half the studies would have a risk ratio less than one and half greater than one if the relationship were not causal. However, it is likely that the case-control studies have recall biases as well as other residual confounding, which would mean that they are consistently estimating a biased association. Evidence of this is that the cohort studies yield a different result.

Other evidence cited by plaintiffs' experts of consistency is that the values of the meta-analyses are similar.<sup>73</sup> As discussed above, since these studies analyze overlapping sets of studies (sometimes essentially the same set of studies), it would be expected that they yield similar estimates of the strength of the associations. The consistency of the estimates across meta-analyses is uninformative for evaluating Hill's consistency of the association criterion.

Another plaintiffs' expert<sup>15</sup> argues that since the Penninkilampi<sup>39</sup> study did not detect statistically significant heterogeneity across the studies, as measured by a statistical non-significant p-value for the  $I^2$  statistic, this is evidence of the consistency of results. This is not a true measure of the consistency of results, for several reasons. The first is that there are more than 25 case-control studies and only three cohort studies. The value of the heterogeneity statistic would be driven by the vast majority of case-control studies, which themselves encompass a four-fold range. Specifically, if the cohort studies were removed and the heterogeneity statistic were recomputed, it would not change by much because only three studies out of 28 were removed. Secondly, a non-significant statistical result for heterogeneity is not proof of lack of heterogeneity. It merely indicates that heterogeneity was not detected. In general, when a result is not statistically significant (i.e., the p-value is greater than 0.05), the only conclusion that can be made is that no difference was detected. It cannot be concluded that there is evidence of no difference because the result could reflect insufficient power to detect a difference. Finally, a test for heterogeneity is not a valid approach for determining whether the results of the case-control studies have different estimates of association than do the cohort studies. The appropriate statistical analysis to address this question is to test for an interaction between exposure and study type (case-control versus cohort). If this interaction term is statistically significant, it means that the association in case-control studies differs from the association in cohort studies, or the observed associations are inconsistent. Such an analysis was performed by Berge et al.,<sup>38</sup> and it was found that case-control studies yield significantly different associations than the cohort studies (p-value = 0.007); looking at the pooled estimates

of association, there was a significant association between perineal talcum powder exposure and ovarian cancer for case-control studies but not for the cohort studies.

A final argument made by plaintiffs' experts is that the level of evidence in the cohort studies is weaker than the level of evidence in the case-control studies.<sup>15,73</sup> The contention is that cohort studies did not probe a woman's talcum powder exposure to the extent that was done for case-control studies. Since most case-control studies and cohort studies reported the association of ever use versus never use of talcum powder in the perineal/genital region, the amount of extensive questioning of talcum powder use likely does not matter. It is relatively easy to measure if someone ever used something and does not require in-depth questioning. Another concern expressed about the cohort studies is that they do not account for the latency period between the time the exposure was initiated and the development of ovarian cancer<sup>15,71,73,74</sup> This is not a valid concern because the date on which the women were asked about the use of talcum powder was not the time they first started being exposed. Many of the case-control studies indicate that women had used talcum powder for a median of 20 years for both cases and controls who reported use.<sup>4,5,14,62</sup> It is unlikely that usage patterns in cohort studies would differ dramatically, and therefore it is likely in cohort studies that the women who used talcum powder had been using it 10-20 or more years at that point. It was also suggested that the follow-up time of the cohort studies is too short to observe ovarian cancer development.<sup>15,71,73,74</sup> The power of studies is driven by the number of observed cases and, as suggested, because there were a sufficient number of cases, especially in the meta-analysis of the cohort studies, the length of follow-up in the cohort studies is not a relevant issue. The cohort data are produced by three high-quality, high-profile cohort studies that have produced a wealth of information yielding hundreds of peer-reviewed publications. There is no evidence that the accepted hierarchy of level of evidence should be reversed when ascertaining whether the association between perineal/genital talcum powder and ovarian cancer is causal or is spurious due to inherent biases and residual confounding.

It is my opinion that the consistency of the association criterion has not been demonstrated. Although the case-control studies generally report risk ratios greater than one, and a little over half of the studies had statistically significant results, the range of the magnitude of the estimate is quite large. Most importantly, there is no consistency between the case-control studies and cohort studies. Meta-analyses of case-control studies yield a statistically significant result, whereas a meta-analysis of the cohort studies indicates there is no statistically significant association. As discussed above, cohort studies eliminate recall bias and participant selection (i.e., control selection) bias that are inherent in case-control studies and lead to spurious associations. Cohort studies yield a higher level of evidence. Hill observed, "I would myself put a good deal of weight upon similar results reached in quite different ways, e.g., prospectively and retrospectively."<sup>1</sup> There is evidence that the observed associations are not

consistent, especially between the retrospective and prospective studies, meaning this criterion does not support a conclusion that the association between perineal/genital talcum powder use and ovarian cancer is causal.

### 6.1.3 DOSE-RESPONSE RELATIONSHIP

The presence of a dose-response relationship provides compelling evidence of causality. Indeed, the notion that the “dose makes the poison” is a fundamental tenet of toxicology. Given that the available data are from observational studies and the association is weak, additional evidence is required to rule out a spurious association, making this criterion more important.

To establish a dose-response relationship, the necessary evidence is increasing risk with increasing dose, statistical significance and consistency. Consistency in this context includes repeated demonstration of the result across different studies, including different study designs, and different measures of dose. Since the data arise from observational studies and there is no standard measure of a dose of talcum powder exposure, surrogate measures of dose are employed. Reasonable choices of dose include the duration of time a woman used talcum powder, the frequency of applications, and the lifetime number of applications that is derived from a combination of duration of use and frequency of use. Although it would not be expected or necessary that all studies or all measures within a study would have a statistically significant dose-response relationship, it would be expected that there would be consistently increasing risk with increasing usage.

The three methods used to measure the perineal/genital talcum powder application dose across the available studies are duration of use measured in years, frequency of application measured as the number of days per week or per month a woman applied the talcum powder and the cumulative lifetime applications, typically a function of duration and frequency of use. The definitions and types of dose measurements are not standardized across the studies. Given this diversity, I concluded it would be most informative to view the results of individual studies that reported a dose-response relationship. Table 1 contains the summary by type of measure for case-control studies. The majority of studies provide no evidence of a dose-relationship – i.e., increasing risk with increasing dose measure that is statistically significant. The only statistically significant results with a dose-relationship are from Wu 2009<sup>61</sup> and Cramer 2016<sup>5</sup> (but only for frequency of use and not for duration or total cumulative applications), and Schildkraut 2016.<sup>4</sup> The reported p-values for the Wu, Cramer and Schildkraut results include women with no perineal/genital talcum powder exposure, which means they may only be significant because of the observed association between ever use and never use of perineal/genital talcum powder, rather than a true dose-response relationship. Specifically, it has been established that there is an association between ever use of perineal talcum powder use and ovarian cancer. In order to determine whether there is a dose-response relationship

among the users of perineal talcum powder, it is important to limit the analysis to only those users of perineal talcum powder. If this is not done, it is hard to interpret the results because it could just again be a measure of ever use versus never use. Once ever use versus never use has been established as an association, to tease out the effects of the amount of use, the analysis needs to be done only in individuals who were exposed to perineal talcum powder products to determine whether there is a dose-response relationship: i.e., whether higher exposure results in a stronger association. A more appropriate test would be to determine if the trend is significant among women who had perineal/genital talcum powder exposure, as reported in Cramer 1999.<sup>35</sup> This is to ensure that the inherent residual confounding and bias that exist in case-control studies is not driving the dose-relationship results. If the dose-response relationship is seen in just the users of talcum powder products, it is less likely that there was substantial recall bias in the association between ever use and never use.

TABLE 1: SUMMARY OF DOSE-RESPONSE RELATIONSHIPS REPORTED IN CASE-CONTROL STUDIES

Study	Frequency Risk ratio (95% CI)	Duration Risk ratio(95% CI)	Total number of applications Risk ratio(95% CI)
Whittemore 1988	none: 1.0 (reference) 1-20/mo: 1.27 (0.82, 1.96) 20+/mo: 1.45 (0.94, 2.22) trend for 30 uses per mo: 1.30 (0.88, 1.92)	none: 1.0 (reference) 1-9 yrs: 1.6 RR (1.00, 2.57) > 10 yrs: 1.11 RR (0.74, 1.65)	
Booth 1989	none: 1.0 (reference) rarely: 0.9 (0.3, 2.4) monthly: 0.7 (0.3, 1.8) weekly: 2.0 (1.3, 3.4) daily: 1.3 (0.8, 1.9)  p-value = 0.05*		
Harlow 1992	none: 1.0 (reference) < 5/mo: 1.5 (0.8, 2.7) 5-29/mo: 1.2 (0.6, 2.2) ≥ 30/mo: 1.8 (1.1, 3.0)	never: 1.0 (reference) < 10 yrs: 1.2 (0.5, 2.6) 10-29 yrs: 1.6 (1.0, 2.7) ≥ 30 yrs: 1.6 (1.0, 2.7)	
Chang 1997	none: 1.00 (reference) < 10/mo: 1.84 (1.24, 2.73) 10-25/mo: 1.13 (0.74, 1.72) > 25/mo: 0.95 (0.61, 1.49)	never: 1.0 (reference) < 30 yrs: 1.70 (1.09, 2.64) 30-40 yrs: 1.44 (0.96, 2.15) > 40 yrs: 0.87 (0.54, 1.38)	
Cook 1997			none: 1.0 (reference) ≤ 2000: 1.8 (0.9, 3.5) 2001-5000: 1.6 (0.9, 2.9) 5001-10000: 1.2 (0.6, 2.4) > 10000: 1.8 (0.9, 3.4)

Study	Frequency Risk ratio (95% CI)	Duration Risk ratio(95% CI)	Total number of applications Risk ratio(95% CI)
Wong 1999		never: 1.0 (reference) 1-9 yrs: 0.9 (0.6, 1.5) 10-19 yrs: 1.4 (0.9, 2.2) ≥ 20 years: 0.9 (0.6, 1.2)	
Cramer 1999		never: 1.0 (reference) < 20 yrs: 1.86 (1.16, 3.00) 20-30 yrs: 1.33 (0.76, 2.30) > 30 yrs: 1.44 (0.91, 2.26)	none: 1.0 (reference) < 3000: 1.84, (1.12, 3.03) 3000-10000: 1.43 (0.84, 2.41) > 10000: 1.43 (0.92, 2.22)
		p-value = 0.48**	p-value = 0.16**
Ness 2000		never: 1.0 (reference) < 1yr: 2.0 (1.0, 4.0) 1-4 yrs: 1.6 (1.1, 2.3) 5-9 yrs: 1.2 (0.8, 1.9) > 10 yrs: 1.2 (1.0, 1.5)	
Mills 2004	none: 1.0 (reference) rarely: 1.34 (0.87, 2.08) 1-3 / week: 1.16 (0.74, 1.81) 4-7 / week: 1.74 (1.14, 2.64)	never: 1.0 (reference) ≤ 3 yrs: 1.01 (0.58, 1.76) 4-12 yrs: 1.86 (1.16, 2.98) 13-30 yrs: 1.45 (0.90, 2.32) > 30 yrs: 1.22 (0.72, 2.08)	never: 1.0 (reference) Q1: 1.03 (0.59, 1.80) Q2: 1.81 (1.10, 2.97) Q3: 1.74 (1.11, 2.73) Q4: 1.06 (0.62, 1.83)
	p-value = 0.015*	p-value = 0.045*	p-value = 0.051*
Merritt 2007		never: 1.0 (reference) 0+ to 10 yrs: 1.13 (0.90, 1.41) 10+ to 25yrs: 1.08 (0.87, 1.34) 25+ yrs: 1.29 (1.04, 1.58)	
		p-value = 0.021*	
Wu 2009			<b>none: 1.00 (reference)</b> <b>≤ 5200: 1.20 (0.77, 1.88)</b> <b>&gt; 5200 to ≤ 15600: 1.38 (0.87, 2.20)</b> <b>&gt; 15600 to ≤ 52000: 1.34(0.89, 2.02)</b> <b>&gt; 52000: 1.99 (1.34, 2.96)</b>  <b>p-value = 0.0004*</b>
Rosenblatt 2011		never: 1.00 (reference) 1-9.9 yrs: 1.39 (0.85, 2.28) 10-19.9 yrs: 1.46 (0.87, 2.45) 20-34.9 yrs: 1.28 (0.78,	none: 1.0 (reference) 1-1599: 1.21 (0.71, 2.06) 1600-4799: 2.08 (1.32, 3.27) 4800-9999: 0.87 (0.50, 1.53) 10000+: 0.87 (0.48, 1.57)

Study	Frequency Risk ratio (95% CI)	Duration Risk ratio(95% CI)	Total number of applications Risk ratio(95% CI)
		2.10)	
		35+ yrs: 0.91 (0.51, 1.62)	
Wu 2015		per 5 yrs: 1.14 (1.09, 1.20)	
Cramer 2016	<b>none: 1.0 (reference)</b> <b>1-7/mo: 1.17 (0.96, 1.44)</b> <b>8-29/mo: 1.37 (1.05, 1.78)</b> <b>≥ 30/mo: 1.46 (1.20, 1.78)</b>  <b>p-value &lt; 0.0001*</b>	never: 1.0 (reference) < 8 yrs: 1.31 (1.03, 1.68) 8-19 yrs: 1.31 (1.02, 1.68) 20-35 yrs: 1.35 (1.07, 1.70) > 35 yrs: 1.33 (1.03, 1.71)  p-value = 0.002*	none: 1.00 ≤ 360: 1.10 (0.83, 1.47) 361 to 1800: 1.38 (1.01, 1.88) 1801 to 7200: 1.16 (0.80, 1.66) > 7200: 1.49 (1.06, 2.10)  p-value = 0.02*
Schildkraut 2016	<b>none: 1.0 (reference)</b> <b>&lt; daily: 1.12 (0.80, 1.58)</b> <b>daily: 1.71 (1.26, 2.33)</b>  <b>p-value &lt; 0.01*</b>	<b>never: 1.0 (reference)</b> <b>&lt; 20 yrs: 1.33 (0.95, 1.86)</b> <b>&gt; 20 yrs: 1.52 (1.11, 2.07)</b>  <b>p-value = 0.02*</b>	<b>none: 1.00</b> <b>&lt; 3600: 1.16 (0.83, 1.63)</b> <b>&gt; 3600: 1.67 (1.23, 2.26)</b>  <b>p-value &lt; 0.01*</b>

The shaded cells indicate studies that reported a dose-response.

Abbreviations: The risk ratio may either be a relative risk (RR) or an odds ratio (OR); CI is confidence interval; mo is month; yrs is years; Q1 is the first quartile; Q2 is the second quartile; Q3 is the third quartile; Q4 is the fourth quartile

\* the test for trend includes the never/none category

\*\* the test for trend does not include the never/none category

The dose-response relationships reported in the cohort studies are summarized in Table 2. Although the Gonzales 2016 study measured frequency of use, this information was not reported in the manuscript.<sup>13</sup> The Gates 2010 study<sup>12</sup> updated the results of the Nurses' Health Study originally reported in Gertig 2000.<sup>10</sup> None of the cohort studies demonstrated a dose-response relationship.

TABLE 2: SUMMARY OF DOSE-RESPONSE RELATIONSHIPS REPORTED IN COHORT STUDIES

Study	Frequency Risk ratio (95% CI)	Duration Risk ratio (95% CI)
Gertig 2000 <sup>10</sup>	none: 1.0 (reference) < 1/week: 1.14 (0.81, 1.59) 1-6/week: 0.99 (0.67, 1.46) daily: 1.12 (0.82, 1.55)	
Houghton 2014 <sup>11</sup>		never: 1.0 (reference) less than 9 years: 1.23 (0.98, 1.54) 10 or more years: 0.98 (0.75, 1.29)
Gates 2010 <sup>12</sup>	none: 1.0 (reference) ≥ 1/week: 1.06 (0.89, 1.28)	

Abbreviations: Risk ratio is either a relative risk (RR) or a hazard ratio (HR); CI is confidence interval

The two most recent meta-analyses and the one pooled analysis are summarized in Table 3. The Terry 2013<sup>20</sup> study showed a slight dose-response relationship with numerically increasing ovarian cancer incidence with increasing frequency as measured by quartiles of total applications. However, this was not found to be statistically significant with a test for trend that did not include never users, the appropriate test. The test for trend is a test to determine whether there is an increase across the different levels. As explained above, in order to determine whether there is increasing association with increasing exposure, only individuals who are exposed should be included in the analysis so that we are sure we are not re-establishing the association between ever exposure versus never exposure. Because the p-value that excluded never users was not statistically significant, there is no increasing association of more perineal talcum powder and ovarian cancer in this study. The Berge 2018<sup>38</sup> study found a significant relationship with the 10-year increments of talcum powder use and with one day of use increment per week of talcum powder and increased ovarian cancer incidence. What this means is that for each additional day per week of use, there was a statistically significant association of 5% increase in relative risk. However, it is not possible to examine whether the relationship is linear because the analysis also includes women who have not used talcum powder, and thus the dose-response finding might be driven by the association between ever use and never use in the case-control studies. The correct analysis would be to determine whether there is an increased association among the women who were exposed to perineal talcum powder and ovarian cancer per each additional day of use per week. Penninkilampi 2018<sup>39</sup> reported the result for duration separately for case-control and cohort studies and reported the total number of applications in the case-control studies. The long-term use (compared to not long-term use, which included never users) was statistically associated in the analysis of the case-control studies, but was not found to be associated in the cohort studies. Although the relative risk ratio is numerically greater for > 3600 total applications compared to < 3600 applications, there is considerable overlap of the corresponding 95% confidence intervals, meaning that these differences are likely not statistically significant.<sup>75</sup> This is so because when there is considerable overlap between two sets of confidence intervals, there is no evidence that the relative risks differ, and if a p-value were computed, it would be non-significant (e.g., greater than 0.05). Note that 3,600 applications roughly correspond to daily use of talcum powder for 10 years. Since there is considerable overlap between the confidence intervals, this supports the possibility that the statistical significance of the long-term use is a consequence of the association between ever use and never use.

TABLE 3: SUMMARY OF DOSE-RESPONSE RELATIONSHIPS REPORTED IN THE META-ANALYSES AND POOLED STUDY

Study	Frequency Risk ratio (95% CI)	Duration Risk ratio (95% CI)	Total number of applications Risk ratio (95% CI)
Terry 2013			none: 1.0 (reference) Q1: 1.14 (1.00, 1.31) Q2: 1.23 (1.08, 1.14) Q3: 1.22 (1.07, 1.40) Q4: 1.32 (1.16, 1.52)  p-value = 0.17*
Berge 2018	none: 1.0 (reference) per 1 time/week: 1.05 (1.04, 1.07)	never: 1.0 (reference) duration per 10 years: 1.16 (1.07, 1.26)	
Penninkilampi 2018 case-control		never: 1.0 (reference) long-term use: 1.29 (1.13, 1.47)	none: 1.0 (reference) < 3600: 1.32 (1.15, 1.50) > 3600: 1.42 (1.25, 1.61)
Penninkilampi 2018 cohort		never: 1.0 (reference) long-term use: 0.98 (0.75, 1.29)	

The shaded cells indicate studies that reported a dose-response.

Abbreviations: Risk ratio is either a relative risk (RR) or an odds ratio (OR); CI is confidence interval; Q1 is the first quartile; Q2 is the second quartile; Q3 is the third quartile; Q4 is the fourth quartile

\* the test for trend does not include the never/none category

Overall, the evidence for a dose-response relationship is not consistent across the case-control studies, with most studies not even numerically demonstrating increasing risk across increasing dose, for whichever measure is used. Examples of this include: (1) Cook 1997, where the risk for  $\leq 2000$  applications (lowest category) was 1.8 and the risk for  $>10,000$  applications (highest category) was also 1.8; and (2) Mills 2004, where the risk for lowest quartile for total applications was 1.03 and the risk for the highest quartile for total applications was 1.06. It also is not consistent across the different measurement types. In fact, some of the case-control studies indicate that more exposure yields a smaller association with ovarian cancer (Booth,<sup>45</sup> Harlow<sup>33</sup>; based on frequency, Chang<sup>51</sup>; for both frequency and duration, Cook,<sup>52</sup> Wong,<sup>55</sup> Cramer 1999<sup>35</sup>; for duration and total number of applications, Ness,<sup>3</sup> Mills<sup>57</sup>; for all three measures, Merritt,<sup>59</sup> Rosenblatt,<sup>62</sup> and Cramer 2016<sup>5</sup>; and for total applications; see Table 1). There is no evidence of a dose-response relationship in the cohort studies, and some studies indicate a lower association with ovarian cancer for higher exposures (Gertig,<sup>10</sup> Houghton<sup>11</sup>; see Table 2). The meta-analyses also do not yield consistent evidence of a dose-response relationship. In the Berge 2018 study, the association observed may be driven by the

association between ever use and never use. This is also true for the long-term result in Penninkilampi 2018 for the case-control studies. There also was a lack of dose-response relationship reported for total number of applications.

Many of plaintiffs' experts claim that most or the majority of studies found a dose-response relationship,<sup>15,70,73</sup> but do not provide a demonstration of this. As can be observed in the tables above, a minority of the studies potentially show a dose-response relationship. It is also argued that the lack of a consistent dose-response relationship could be explained by a threshold effect.<sup>70,73</sup> However, if there is a threshold effect, which is very uncommon in cancer, studies should yield a consistent result for what the threshold is, along with biological evidence (cell line and animal models) that this is the type of the relationship. In particular, it seems unlikely that if a woman used perineal/genital talcum powder once, she has the same increased risk of developing ovarian cancer as a woman who used perineal/genital powder daily for 20 years, even assuming there is a causal relationship. Looking at the data, this would be the only plausible threshold value.

One of the studies that fails to find a dose-response relationship is Huncharek 2003,<sup>36</sup> which reported a relative risk for the association between the lowest level of exposure and ovarian cancer of 1.83, versus an association of 1.21 for the highest level of exposure. This study has been criticized by plaintiffs' expert Dr. Zambelli-Weiner.<sup>76</sup> While I agree that there are numerous errata in the manuscript, most of which are superficial and not uncommon in scientific papers, the analyses performed by Zambelli-Weiner also fail to establish a dose-response relationship. Specifically, although the estimates of the risk ratios reported in the manuscript cannot be replicated from the information provided by the authors, the analyses performed by plaintiffs' expert as part of her effort to illustrate the posited flaws in the Huncharek paper had different estimates of the risk ratios but still did not provide evidence of a dose-response relationship.

In summary, there is no evidence of a dose-response relationship (linear or threshold) across the available information. The results across the different measures are not consistent and only a few of these demonstrate a relationship. The few studies that suggested a dose-response were case-control studies. None of the cohort studies observed a dose-response relationship, and cohort studies provide a higher level of evidence than do case-control studies.

#### 6.1.4 TEMPORALITY

The question of temporality is whether there is evidence that the perineal/genital talcum powder exposure occurred prior to the development of ovarian cancer. This is clearly true for the cohort studies in that when women were asked about their exposure, many had been using talcum powder products for years. Women who had developed ovarian cancer prior to being

asked about their talcum powder exposure were excluded from the analyses. For the case-control studies, it is also likely that women had been exposed to perineal/genital talcum powder starting years before their ovarian cancer was diagnosed. Although it might be true that some of the women started using talcum powder as a consequence of their ovarian cancer, e.g., to alleviate side effects of treatment, and incorrectly reported they used it prior to their cancer, this is likely a small proportion and would not have a substantial impact on the reported association. This is the one criterion that must be satisfied in order to consider whether an association is a causal relationship because no association can be considered causal if the outcome occurs before the exposure. This is a necessary condition to be met, but it alone is not sufficient for establishing causation. Overall, I find that this criterion has been satisfied.

#### 6.1.5 OTHER CRITERIA

The other Hill criteria have somewhat less focus on human studies and are briefly reviewed here. **Specificity** implies that there is essentially a one-to-one correspondence between a particular exposure and a specific disease. If there is evidence for this, it would increase the likelihood that an observed association between perineal/genital talcum powder exposure and ovarian cancer is causal. However, as discussed above, this has less relevance because it is known that diseases arise from a complex process, meaning that it would not be expected that all ovarian cancers would arise from a single cause. Another aspect of specificity would be that only perineal/genital talcum powder exposure would be associated with the development of ovarian cancer versus other uses of talcum powder. However, this is not the case. There have been case-control studies that observed associations of similar magnitude of non-perineal/genital talcum powder use and ovarian cancer, most of which were statistically significant.<sup>3,4,39,61</sup> Other lifestyle choices that have been found to be associated with ovarian cancer, with similar or greater associations than perineal/genital talcum powder use, include douching<sup>13</sup> and coffee consumption.<sup>43</sup> This illustrates the difficulty of establishing whether an observed association of a lifestyle choice and a disease is causal or spurious due to residual confounding or inherent biases in observational study design. Overall, there is no evidence provided by this criterion with respect to whether the association between perineal/genital talcum powder use and ovarian cancer is causal.

The biological mechanism that has been proposed is that particles within talcum powder can migrate up the genital tract to the fallopian tubes and ovaries.<sup>15,70,71,73,74</sup> Once there, it purportedly elicits an inflammatory response that initiates cancer development. Evidence for the **biological plausibility** of this would require a demonstration that only women who use perineal/genital talcum powder have embedded particles in ovary tissue, and the women who use more talcum powder have a higher risk (and perhaps greater quantity) of embedded particles. Another aspect that would need to be shown is that any inflammation associated with the development of ovarian cancer is observed in ovarian tissue that has embedded talcum

powder particles. The current state of cancer research would allow these aspects to be demonstrated if, in fact, they occurred. In addition, to establish biologic plausibility, there would need to be extremely strong effects in cell line experiments as well as animal models that isolate components of the proposed mechanism of action.

None of this evidence exists, however. While there is strong evidence that chronic inflammation can give rise to carcinogenesis in various different cancers, this is not an established mechanism for ovarian cancer. Moreover, there are no data of ongoing or chronic inflammation in perineal talc users, whether in the ovary or otherwise, or that inflammation is occurring in the presence of talc in ovarian tissue. In fact, where talc has been found in ovarian tissue, no inflammation has been found.<sup>77</sup> Further, studies looking at pelvic inflammatory disease (PID) and the effect of aspirin and NSAIDs have not shown a consistent effect.<sup>59,61,78-84</sup> What is missing is evidence that sufficient quantities of talcum particles from perineal/genital application migrate to the fallopian tubes and ovaries to cause chronic inflammation that gives rise to the development of ovarian cancer. At the present time, there are no animal models that demonstrate carcinogenesis from perineal/genital talcum powder application. Again, although there is some evidence for individual components of the proposed process (i.e., chronic inflammation gives rise to carcinogenesis in a variety of cancers), there is no demonstration for the entire process from perineal/genital talcum powder exposure to the development of ovarian cancer that has been proposed. In cancer, if large and definitive effects are not observed in cell line experiments and animal models, there likely will not be an effect in humans. For example, in cancer drug development, all drugs tested in humans have compelling cell line, animal data, and sometimes translational data, and yet, most drugs ultimately are not found to provide human benefit. All of plaintiffs' experts posit this mechanism as biologic plausibility, without providing a reference to a cogent biological mechanism or evidence by which external perineal application of talcum powder induces ovarian cancer. I understand that plaintiffs' experts rely on a study by Dr. Saed that conducted in vitro studies that involved placing talc on certain cell lines. Although the details of the study are outside my area of expertise, I understand based on his deposition that there are many gaps and irregularities in his work and that it would not provide a mechanism satisfying this criterion.<sup>85</sup> From my review of the pre-clinical data, there is no evidence that definitively supports the hypothesized mechanism of action for how perineal/genital application of talcum powder leads to the development of ovarian cancer. Such evidence would include talcum particles embedded in ovaries and found along the reproductive tract, with inflammation of ovaries around the embedded particles, and animal models that demonstrate the development of ovarian cancer when their genital region is exposed to talcum powder. This criterion is not sufficiently demonstrated.

The **experiment** criterion has not been met. As discussed above, it is not feasible to conduct a randomized trial of perineal/genital talcum powder exposure and ovarian cancer. Likewise, it also is not feasible to perform an experiment or study where a group of women who use talcum powder in the perineal/genital region cease the exposure and another group does not cease the exposure and they are followed over time. As such, there are no human experimental data available that would support a causal relationship. This criterion is uninformative with respect to whether the association between perineal/genital talcum powder exposure and ovarian cancer is causal.

There is no analogy for perineal/genital talcum powder exposure and ovarian cancer. Some plaintiffs' experts posit an **analogy** with asbestos, either through the mechanism by which asbestos causes ovarian cancer<sup>15,71,74</sup> or the chemical similarity between talc and asbestos.<sup>70,73</sup> But for this analogy to hold (and moreover, if asbestos is present in talc), one would expect an association between talc exposure and mesothelioma, which is a signature disease for asbestos. But plaintiffs' experts have not identified any studies showing that talc users are at an increased risk of developing mesothelioma. And studies of miners and millers of talc – who regularly inhale talc – have not reported any such association.<sup>86-88</sup>

Dr. Wolf concludes that the analogy criterion is met because of similarity with other cancer risk factors through the process where cancer is initiated by a foreign agent. These include smoking and lung cancer, asbestos and mesothelioma and ovarian cancer, sun exposure and skin cancer, and HPV and cervical cancer. The latter two are not examples of a foreign body causing inflammation: sun exposure causes DNA damage and HPV is a viral infection. In any event, the proposed analogy of a foreign body causing a cancer is too broad for the analogy to be satisfied for perineal/genital talcum powder exposure and ovarian cancer risk. This criterion has not been met for perineal/genital talcum powder exposure and ovarian cancer.

The **coherence** criterion is vague and overlaps considerably with other Hill criteria. One aspect of coherence that has not been met is that if perineal/genital talcum powder exposure were a causal risk factor for ovarian cancer, it would be expected that talcum powder usage that is more proximal to the fallopian tubes and ovaries would be associated with ovarian cancer. In addition, it would be expected that women who use talcum powder on diaphragms or have partners who used talc dusted condoms would have a stronger association with ovarian cancer. The studies that investigated these associations actually found no increased risk or a protective relationship, meaning that relative risks less than one were reported.<sup>40</sup> In addition, if it were true that talcum powder particles cause cancer through inflammation, it would be expected that inhalation of talcum powder would result in increased lung cancer, which has not been observed. It would also be expected that perineal talc powder exposure would be associated with vaginal, cervical and endometrial cancer. However, I am not aware of any evidence of this

or of any theory as to why talc use would only affect the ovaries and not the other sites along the reproductive tract leading from the perineal to the ovaries. Finally, given that ovarian cancer has several subtypes that are often researched as separate diseases and may well have different causes, there is no coherence to the extent plaintiffs' experts contend that perineal talc use increases the risk of multiple subtypes of ovarian cancer. Hence, this criterion has not been met in terms of providing evidence of a causal association between perineal/genital talcum powder exposure and ovarian cancer.

## 7 EVALUATION OF DR. SMITH-BINDMAN'S META-ANALYSIS AND EXPERT REPORT

Two of plaintiffs' experts performed their own meta-analyses: Drs. Siemiatycki and Smith-Bindman. The results of Dr. Siemiatycki's analysis yielded an association of 1.28 with a 95% confidence interval of 1.19 to 1.38. He also performed a sensitivity analysis, and the resulting risk ratios were 1.26 to 1.30. The results of Dr. Smith-Bindman's meta-analysis were an association of 1.43 (95% confidence interval of 1.15 to 1.71) between regular perineal exposure and any ovarian cancer and 1.52 (95% confidence interval of 1.15 to 1.88) between regular perineal exposure and invasive serous ovarian cancer. Dr. Siemiatycki's results align with the other existing meta-analyses, whereas Dr. Smith-Bindman's results are considerably different. Since this study was not peer-reviewed, I critically reviewed this meta-analysis for explanations for the difference, as well as for the validity of the results.

### 7.1 SUBGROUP ANALYSIS AND HARKING

The analysis performed by Dr. Smith-Bindman is a post-hoc subgroup analysis. There is evidence in the literature regarding how subgroup analyses are prone to spurious results.<sup>89-92</sup> Post-hoc subgroup analyses refer to those in which "hypotheses being tested are not specified before any examination of the data."<sup>90</sup> Wang et al. state that "[s]uch analyses are of particular concern because it is often unclear how many were undertaken and whether some were motivated by inspection of the data."<sup>90</sup> Stallones observes that "[f]or the most part, the associations discovered in a subgroup analysis are large enough to attract our attention; indeed the analysis was probably engineered to maximize that value."<sup>89</sup> The subgroup selected by Dr. Smith-Bindman to perform her meta-analysis were women who were *regular users* and developed *invasive serous ovarian* cancer. Dr. Smith-Bindman claims it is an advantage to have a very narrow research question, and this is often true. However, it is not valid to have such a narrow question after having reviewed the data beforehand and then proposing what study will be done, especially since the subsequent study is based on the same data that were used to generate the new question. All the previous meta-analyses included most, if not all, publications on the association between perineal talcum powder exposure and ovarian cancer,

and her analysis did not uncover any new studies to analyze. Hence, this is essentially a subgroup analysis of the previous meta-analyses, motivated by findings in the previous meta-analyses. It should be noted that in her deposition taken on February 7, 2019, Dr. Smith-Bindman states that she did a stratified analysis rather than a subgroup analysis. However, a stratified analysis is one that reports the results for all the strata, not just for one particular stratum. Specifically, if there were a stratified analysis, there should be summary risk ratios for non-regular users of perineal talcum powder and for non-serous ovarian cancer. Since she did not provide these, this cannot be considered a stratified analysis, but is rather a subgroup analysis with the subgroups being: (1) individuals who were regular users of perineal talcum powder; and (2) cases who developed serous ovarian cancer.

A related concern with performing a subgroup analysis is HARKing, Hypothesizing After the Results are Known. Kerr<sup>93</sup> describes HARKing as "...hypotheses presented as a priori rationales for the research to be reported; that is, hypotheses that ostensibly guided the design of that research and for which the data to be described provide an independent empirical test." There are many issues that arise due to HARKing. One relevant drawback is that the proposed hypothesis cannot fail. Specifically, when an investigator knows the results of the study in advance and proposes a hypothesis consistent with those results, there is no possibility of finding a non-significant result; the fix is in. Clearly, this is not good scientific methodology. A second relevant drawback indicated by Kerr is that "HARKing promotes narrow (i.e., context and paradigm bound) new theory." A primary research goal is to develop a general theory, and HARKing may encourage a focus on explaining the narrow effect at the cost of ignoring the broader set of potentially relevant prior findings. This is applicable here since now the focus is on invasive ovarian cancer without firmly establishing lack of association with other types of ovarian cancer.

Overall, the scientific validity of focusing on a subset question after having reviewed all the data at hand is questionable. Dr. Smith-Bindman did not posit any biological plausibility as to why invasive serous ovarian cancer would be more likely to be the result of perineal talcum powder exposure. Hence, the results of her analyses are at best hypothesis-generating and cannot be determined as definitive. Essentially, her results raise the hypothesis that the association between regular users of perineal talcum powder and invasive serous cancer may be about 1.5. However, given the concerns with subgroup analyses and HARKing, this cannot be taken as evidence that the association is higher in this group, especially in light of the fact that this is the only study to find this, and it was not peer-reviewed. It should also be noted that this does not provide any evidence regarding the causality question since it is only a subgroup meta-analysis, and thus only pertains to the strength of the association within the Hill framework. Finally, these results are in contrast to what I illustrate in Table 6 below, where there is no coherent pattern supporting a stronger association between perineal talcum powder and serous ovarian

cancer compared to any ovarian cancer. It likely arises because there was further subgrouping to women who were deemed by Dr. Smith-Bindman to be regular users of perineal talcum powder.

## 7.2 METHODOLOGICAL ISSUES

There is also a concern that the results of Dr. Smith-Bindman's analysis cannot be reproduced. I tried to match the numbers that were used in the meta-analysis that are reported in her expert report in Figures 2 and 3.<sup>70</sup> Table 3 and Table 4 show the results in her report and my attempts to match the values in the original manuscripts. As can be seen, none of the confidence interval numbers can be found in the original manuscripts. This is concerning because either the number of individuals in each group or the confidence intervals are used as part of the calculation in the meta-analysis to yield a summary risk ratio, and thus errors in abstraction directly bear on the reliability of the study's results. As stated by Dr. Smith-Bindman herself in her deposition on February 7, 2019, "I think one of the hallmarks of doing a systematic review is, in fact, to have several people abstract the data points so that you can be assured that there are – that they're done as accurately as possible, with the understanding of a single data abstraction by a single person can never be perfect."<sup>94</sup> Later, when Dr. Smith-Bindman was asked who calculated the confidence intervals that appeared in Figure 2 of her expert report, she responded, "To the best of my knowledge, these confidence intervals came from the primary publications."<sup>94</sup> After a telephone call with her colleague, Dr. Jane Hall, on the evening of February 7, 2019, however, Dr. Smith-Bindman testified in her deposition on February 8, 2019, "I was quite surprised that they weren't exactly the same. They were not meaningfully different, but there was a very slight shift in the ones that are in my report. I mean, I asked Dr. Jane [sic] why that was the case. And in fact, the numbers are calculated using the standard errors in the confidence intervals and the sample size which very slightly shifts it from the reported number. So you were correct when you said the numbers are not exactly the same, and she explained that that's why that's the case."<sup>95</sup>

The number of individuals in each group did not appear to be available, as indicated by the exchange between Dr. Smith-Bindman and Dr. Hall, the statistician.<sup>2</sup> The number of individuals in each group is needed to arrive at the weights that will be used when combining the reported risk ratios in the publications that are part of the meta-analysis. In the email on September 24 referenced above, Dr. Hall indicated that she would do her best to estimate the missing information, and Dr. Smith-Bindman confirmed that she instructed Dr. Hall that "when the raw numbers for th[e] missing proportions were not available, to do her best to estimate those."<sup>94</sup> It

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<sup>2</sup> This is an email with the following information (1) From: Jane Hall [drjanehall@janehall-biomed.com](mailto:drjanehall@janehall-biomed.com), (2) Date: Monday, September 24, 2018 at 11:44 PM, (3) To: "Smith-Bindman, Rebecca" <Rebecca.Smith-Bindman@ucsf.edu>, (4) Cc: "Wang, Ralph" [Ralph.Wang@ucsf.edu](mailto:Ralph.Wang@ucsf.edu) and (5) Subject: Forest Plots - Data Decisions.

is also stated in Dr. Smith-Bindman's report that the SE (standard error) was estimated using the relationship: 95% confidence interval for the OR = effect size  $\pm 1.96 \times \text{SE}$ .<sup>70</sup> This would be an incorrect calculation because the 95% confidence interval for the natural log of the risk ratio obeys the stated relationship: 95% confidence interval for  $\ln(\text{OR}) = \text{effect size} \pm 1.96 \text{ SE}$ .<sup>96</sup> What this means is one must take the  $\ln$ , or natural log, of the 95% confidence interval to get the SE, which is on the log scale. All calculations need to be done on the  $\ln$  scale and then transformed back to the original scale at the end. It is not clear what was done to arrive at the estimates for the risk ratios provided by Dr. Smith-Bindman in her report because of the incorrect confidence intervals reported in Figures 2 and 3, which should be the values that were used in the calculation taken from the original manuscripts, and because of the incorrect statement of how to obtain SE for the OR. There is no clear documentation for how the weights were derived to arrive at the estimates of the ORs in Dr. Smith-Bindman's report other than Dr. Hall's statement in an email that she would do her best to estimate them.

TABLE 4: RESULTS REPORTED IN FIGURE 2 OF SMITH-BINDMAN EXPERT REPORT COMPARED TO THE ORIGINAL MANUSCRIPTS

Cited Study	In report	In publication	Regular use definition
Booth 1989	1.30 (0.75, 1.85)	1.30 (0.8, 1.9)	Daily
Chang 1997	0.95 (0.51, 1.39)	0.951 (0.61, 1.49)	> 25 after bath talc use per month
Cook 1997	1.80 (0.55, 3.05)	1.8 (0.9, 3.4)	> 10,000 lifetime applications
Cramer 2016	1.49 (0.97, 2.01)	1.49 (1.06, 2.10)	> 72000 applications <b>[note that daily use was 1.46 (0.76, 1.48)]</b>
Gertig 2000	1.12 (0.76, 1.48)	1.12 (0.82, 1.55)	Daily
Harlow 1992	1.80 (0.85, 2.75)	1.8 (1.0, 3.0)	Total applications > 10,000 <b>[applications <math>\geq 30</math>/ month: 1.8 (1.1, 3.0)]</b>
Mills 2004	1.74 (0.93, 2.55)	1.74 (1.14, 2.64)	4-7 times per week
Schildkraut 2016	1.71 (1.18, 2.24)	1.71 (1.26, 2.33)	Any genital use daily
Whittemore 1988	1.45 (0.81, 2.09)	1.45 (0.94, 2.22)	20+ applications/month
Wu 2009	2.08 (1.14, 3.02)	2.08 (1.34, 3.23)	> 20 years and > 30 times/month

TABLE 5: RESULTS REPORTED IN FIGURE 3 OF SMITH-BINDMAN EXPERT REPORT COMPARED TO THE ORIGINAL MANUSCRIPTS

Cited Study	In report	In publication	Histology
Chang 1997	1.51 (0.7, 1.96)	1.51 (1.13, 2.02)	invasive ovarian cancer <b>[Serous reported as 1.336 (0.96, 1.85)]</b>
Cook 1997	1.80 (0.55, 3.05)	1.7 (1.1, 2.5)	Serous <b>[NOTE: same estimate as Figure 2 in report]</b>
Cramer 2016	1.54 (1.08, 2.00)	1.54 (1.15, 2.07)	Serous; > 24 talc years
Gertig 2000	1.49 (0.86, 2.12)	1.49 (0.98, 2.26)	Serous; ever daily use

Another concern is that it does not appear as though all studies were included in the analysis. In particular, it can be seen from Table 2 that the Rosenblatt 2011 study included risk ratio estimates based on the total number of applications. This study appears to have been initially considered for Dr. Smith-Bindman's analysis but ultimately excluded, although she did include Harlow 1992, which also only had total number of applications available. As seen in Table 4, the value used from Harlow 1992 is from "Total applications > 10,000" which had a OR of 1.8. The Rosenblatt 2011<sup>62</sup> study has the same category, "10,000+" (see also Table 2), and it reported an OR of 0.87. Again, this lower OR was not included in the meta-analysis performed by Dr. Smith-Bindman, and during her deposition, she was not able to explain why this was the case.<sup>94</sup> In fact, the only explanation provided was that exclusion of the Rosenblatt 2011 study did not impact the overall results.<sup>94</sup> This is false – the reported negative association in Rosenblatt 2011 would have lowered Dr. Smith-Bindman's reported odds ratios, as shown in the raw data from Dr. Hall that Dr. Smith-Bindman produced.<sup>97</sup>

The definition of what was considered to be regular use is also unclear. For example, Harlow 1992 and Cramer 2016 included values for the frequency of applications so that the value of "daily use," which Dr. Smith-Bindman indicated was the definition of regular use, could have been used. Instead, a decision was made to use the highest category for total number of applications instead for these studies. In the case of Cramer 2016, the risk ratio for daily use was 1.46, compared to the 1.49 for > 72000 total applications, which was used in the meta-analysis. In addition, it was stated that serous ovarian cancer was of interest when available. However, the risk ratio of 1.51 for invasive ovarian cancer was used from the Chang 1997 study, rather than the lower risk ratio of 1.336 for serous cancer in the same report. From her deposition, it is not clear why the higher value for invasive ovarian cancer was used rather than the value for serous ovarian cancer, which was the group of interest.

Other minor concerns raise questions about the experience of the Dr. Smith-Bindman and her statistical consultant in performing meta-analyses. Generally, the investigators do not appear to be aware of the correct technical terms that are used in such analyses. What is called a "Forrest Plot" is actually denoted as a forest (as in trees) plot. Also, Dr. Smith-Bindman technically performed a meta-analysis since she generated a quantitative estimate of the association between perineal talcum powder exposure and ovarian cancer. She states that she is performing a systematic review, which would not involve generating such a number. These are minor issues and do not impact the reported results, but merely raises the issue of how much experience the investigators (Dr. Smith-Bindman and the statistical consultant) have with respect to performing meta-analyses.

### 7.3 OTHER NOTED MISSTATEMENTS IN THE REPORT

There are several other misstatements or misunderstandings in Dr. Smith-Bindman's expert report. One is confusing the Bradford Hill criterion of strength of association with impact on public health. Dr. Smith-Bindman states:

"It is frequently argued that the larger an apparent association, the more likely the association is to be real (causal) and important for epidemiological assessment. This would suggest that an OR of 2.0 is more likely to indicate causality and importance than an OR of 1.5. While this is often argued, I do not believe this is necessarily the case. If a risk factor increases the risk of disease by 50%, and the exposure is common, it will have a far greater impact on a number of people, in comparison to a rare exposure that has a higher associated OR. And if the association is truly one that increases risk by 50%, then this is the magnitude of the association that will be detected. It is not intuitive that if an exposure increases a risk by 50%, this difference is not discoverable compared with an exposure that increases risk by 100%."<sup>70</sup>

Dr. Smith-Bindman's statement misses the import of Bradford Hill with respect to strength of association. What Hill was expressing was the concern that smaller observed associations are more likely to arise from confounding rather than causal effects and that more care therefore needs to be taken to rule out confounding. Dr. Smith-Bindman seems to believe that strength of association relates to: (1) the ability to detect such an effect, and (2) the public health impact. This is erroneous. The strength of association criterion is not due to the ability to detect smaller effects. There are many associations reported in the literature, including the association between perineal talcum powder exposure and ovarian cancer, that have been "detected," meaning they were found to be statistically significant. That does not have anything to do with "strength" of the association. In addition, for an association to have a public health benefit, it must be causal. As explained previously, if the association is due to confounding, removing it would have no impact on public health.

Dr. Smith-Bindman also claims that the cohort studies provide a lower quality of evidence than do the case-control studies. According to Dr. Smith-Bindman:

"The small number of cohort studies I found on the relationship between talcum powder products exposure and ovarian cancer did not focus on the details of this topic. While they may have included questions about talcum powder exposure, they were not sufficiently nuanced to provide meaningful information. Thus, in most of the cohort studies I found, measurements of exposure were poor, not specific, or inaccurate. Further, several had very short follow-up periods with data or information about the

time before the cancer occurred. This negates an advantage of cohort studies, which is being able to learn about exposures before the cancer, eliminating recall bias.”<sup>70</sup>

There is no evidence provided or cited that the questions used in the cohort studies were any more or less valid than those used in the case-control studies. In some cases, there were similar types of questions used in both of the study designs. Hence, there is a lack of basis for her statement that the measurements of exposure in the cohort studies were “poor, not specific, or inaccurate.” As I mentioned above, the length of follow-up is not an issue because the power is driven by the number of ovarian cancer cases that were observed, which was adequate, and there is evidence that the perineal talcum powder exposure was initiated decades before the women were assessed for their exposure. It should be noted that all these differences between case-control studies and cohort studies exist across all scientific questions for which case-control and cohort studies are performed, not just the association between perineal talcum powder exposure and ovarian cancer. As I cite above, there is evidence in the literature that cohort studies provide less biased information than do case-control studies, and I have not found instances where the opposite is argued. It can be the case that a specific case-control study is performed better than a specific cohort study. However, the cohort studies used for evaluating the association between perineal talcum powder exposure and ovarian cancer are acknowledged to be high-quality studies, which have produced a multitude of publications. There is no basis for believing that, in this particular instance (evaluation of the association between perineal talcum powder exposure and ovarian cancer), case-control studies provide a stronger level of evidence than cohort studies.

It is also stated in her report that “[t]he **systematic reviews provide a remarkably consistent estimate of an approximately 30% increase in the risk of ovarian cancer associated with any talc powder products use.** The studies summarized in the systematic reviews reported consistent results with little variability and closely overlapping estimates for ovarian cancer risk due to talc use.”<sup>70</sup> This is not surprising given that the systematic reviews were all based on subsets of the same set of studies. More recent systematic reviews/meta-analyses included all the studies included in earlier meta-analyses and meta-analyses performed at the same time period (e.g., Berge and Penninkilampi) and used essentially the same sets of studies. Hence, it would be expected that all the estimates are similar. This is not evidence of consistency of results in support of a causal association.

## 7.4 SUMMARY

Overall, the analysis provided by Dr. Smith-Bindman does not provide additional evidence in support of causality of perineal talcum powder exposure and ovarian cancer. Her analysis merely reports an association that is higher than that of other meta-analyses and suffers from the limitations of subgroup analyses and HARKing, which are known to lead to spurious

findings. There is no additional evidence provided in support of a causal association. There is also a methodological concern that the confidence intervals were calculated improperly. Furthermore, there is no protocol available that outlines the steps for how the studies were selected, what was selected as the definition of regular use of perineal talcum powder, and how the weights were calculated in the meta-analysis. Finally, there are other misstatements/misunderstandings in her report, of which I have highlighted a few above. Overall, I do not believe that the odds ratios from Dr. Smith-Bindman's analysis can be reproduced.

## 8 OTHER CONSIDERATIONS

There were a few other general considerations that formed my opinion. One is whether there is evidence that there is a stronger relationship with the most common histologic subtype of epithelial ovarian cancer: serous cancer. Although this is a subgroup analysis that has all the issues of a subgroup analysis, I address this theory because it appears in several of plaintiffs' experts' reports.<sup>15,70,71,73</sup> Next, I evaluated whether there is evidence of residual confounding within the observational studies. Finally, I looked at the evidence that has emerged since the IARC 2010 report to determine whether there is more evidence now than there was at the time of the report to support a conclusion that a causal relationship exists between perineal/genital talcum powder exposure and ovarian cancer.

### 8.1 SEROUS OVARIAN CANCER

The studies I used to determine whether there is a stronger relationship for serous ovarian cancer versus the association reported for all ovarian cancer are the two recent meta-analyses (Berge 2018<sup>38</sup> and Penninkilampi 2018<sup>39</sup>), the pooled study (Terry 2013<sup>20</sup>), two recent large case-control studies (Schildkraut 2016<sup>4</sup>, Cramer 2016<sup>5</sup>), and three cohort study reports (Gertig 2000<sup>10</sup>, Houghton 2014<sup>11</sup>, Gates 2010<sup>12</sup>). The data are summarized in Table 4. There is only one study that reported a significant increase in the relative risk, the Gertig 2000 report of the Nurses' Health Study. Interestingly, an updated report of the results from the Nurses' Health Study (Gates 2010) no longer shows a difference between the relative risk for all ovarian cancer and serous cancer. The estimates of the relative risks between perineal/genital talcum powder exposure and any type of ovarian cancer and serous ovarian cancer are the same.

It should be noted that most of plaintiffs' experts<sup>15,70,71,73</sup> specifically call out the association between serous cancer and ovarian cancer, with some indicating it is a stronger association than that observed for all ovarian cancer or the other ovarian cancer subtypes. There are also differing conclusions between Drs. Siemiatycki<sup>74</sup> and Dr. Smith-Bindman<sup>70</sup> based upon their independent meta-analyses. Dr. Siemiatycki notes that "...from study to study, it is not always the same subtype that seems to have the highest or lowest relative risks." He further observes,

“[t]hus there is no persuasive evidence in these studies, taken as a whole that the effect of talc differs by histologic subtype of epithelial ovarian cancer.”<sup>74</sup> This differs from the conclusion of Dr. Smith-Bindman who, as discussed above, states, “it is my opinion that women exposed to perineal talc powder products on a regular basis have about a 50% increase in their subsequent risk of developing invasive serous ovarian cancer...” Regarding other types of ovarian cancer, she states that, “[i]n my opinion, this risk is likely overall in about the same range as for serous cancer, but I would estimate slightly less at 40% increased risk.”<sup>70</sup> My conclusion is similar to that of Dr. Siemiatycki. Based on the information in Table 6, there is no evidence that the association differs considerably between perineal/genital talcum powder exposure and any ovarian cancer or serous ovarian cancer. Only Gertig<sup>10</sup> showed a considerably different estimate for serous ovarian cancer (OR = 1.40, 95% CI: 1.02, 1.91) but when the results were updated after more follow-up in Gates<sup>12</sup>, this difference no longer existed (OR = 1.06, 95% CI: 0.84, 1.35), indicating that the first difference was likely spurious.

TABLE 6: COMPARISON OF OBSERVED ASSOCIATIONS BETWEEN PERINEAL/GENITAL TALCUM POWDER EXPOSURES AND OVARIAN CANCER AMONG STUDIES

<b>Study</b>	<b>Any Ovarian Cancer</b> Risk ratio (95% CI)	<b>Serous Ovarian Cancer</b> Risk ratio (95% CI)
<b>Meta-analyses</b>		
Berge 2018	1.22 (1.13, 1.30)	
Penninkilampi 2018		
case-control	1.35 (1.27, 1.43)	1.34 (1.23, 1.47)
cohort	1.06 (0.90, 1.25)	1.19 (0.97, 1.47)
<b>Pooled</b>		
Terry 2013	1.24 (1.15, 1.33)	1.20 (1.09, 1.32)
<b>Case-Control</b>		
Schildkraut 2016	1.39 (1.10, 1.76)	1.38 (1.03, 1.85)
Cramer 2016	1.33 (1.16, 1.52)	1.42 (1.19, 1.69)
<b>Cohort</b>		
Gertig 2000	1.09 (0.86, 1.37)	<b>1.40 (1.02, 1.91)</b>
Houghton 2014	1.12 (0.92, 1.36)	1.13 (0.84, 1.51)
Gates 2010	1.06 (0.89, 1.28)	1.06 (0.84, 1.35)

Abbreviation: Risk ratio is either a relative risk (RR), an odds ratio (OR), or a hazard ratio (HR); CI is confidence interval

Dr. McTiernan observes that it is difficult to compare the results of the Gertig 2000<sup>10</sup> and Gates 2010<sup>12</sup> Nurses' Health Study publications. She states, “The first publication used ‘never use’ as the comparison and found a statistically significant effect for risk of serous ovarian cancer with any use of talcum powder products. The third publication combined ‘never use’ and ‘less than once per week’ into one referent category. If low frequency use increases risk of ovarian

cancer, which is entirely plausible, combining such women with never users will seriously underestimate the true relative risk associated with use of talcum powder products.”<sup>15</sup> I do not see this as a particular problem. If there is a threshold effect, as has been put forward by some of plaintiffs’ experts, then grouping no use with infrequent use should better detect an association because placing the infrequent users with regular users would make the association weaker if infrequent use is not above the threshold value. If there is a threshold value, grouping the participants this way would make it more likely to observe a significant association because it is assured that participants in the user group received enough exposure to cause disease and that the exposed group is not diluted by people with exposures at levels that would not cause disease. It should also be noted that Dr. Smith-Bindman only used participants who had regular use versus a control group with no use. Although this split is a bit cleaner because she did not just use individuals who used less than regularly, it is the same concept in that, if a threshold relationship is posited, then less than regular users should not be in the exposed group. Finally, the overall results of Gertig 2000 and Gates 2010 with respect to the association between perineal talcum powder use and ovarian cancer did not differ much: the risk ratio reported in Gertig 2000 was 1.09 and that reported in Gates 2010 was 1.06, both non-significant. Given the small change in this risk ratio, it is likely that the large change in the risk ratio for the association with serous cancer (1.40 in Gertig compared to 1.06 in Gates 2010) is not due to the different definition of the comparator groups.

## 8.2 EVIDENCE OF RESIDUAL CONFOUNDING AND BIAS

All studies have varying degrees of error. Common sources of error include confounding, biases and random chance. The error due to random chance is only examined if there is no systematic error, such as confounding or biases. Systematic error is of concern because it means estimates of association are not estimating the true underlying association. As a result, there may be no true association between an exposure and a disease but due to confounding, an association is observed. For example, there may be an association between having gray hair and ovarian cancer. This is not a true association. In reality, a woman with gray hair compared to a woman (of the same age) without gray hair would have the same likelihood of developing ovarian cancer. The underlying confounder is age. Biases occur when there are systematic issues within the study design, such as how cases are selected or recall bias. When a relatively weak association between an exposure and disease is observed in observational studies, a thorough evaluation must be made to rule out residual confounding and biases. If there is evidence of confounding and biases in the observational studies, then the importance of satisfying the other Hill criteria increases; in particular, there needs to be strong biological evidence that the exposure directly leads to the disease.<sup>31,67</sup>

There are several known factors associated with ovarian cancer. Some factors that have been established in the field include age, nulliparity status, use of oral contraceptives and family history of ovarian cancer. Older age is associated with increased risk of ovarian cancer. Women who are nulliparous have a higher risk of ovarian cancer. If a woman has used oral contraceptives for five years or longer, this reduces the risk of ovarian cancer. A family history of ovarian cancer increases the risk of ovarian cancer.<sup>98-100</sup> In all studies of the association between perineal talcum powder exposure and ovarian cancer that measured these established risk factors, there were differences between the cases and controls. In all instances of difference, the cases had a higher burden of ovarian cancer risk factors. The cases were older on average, even in some case-control studies that matched controls on age. The cases were more likely to be nulliparous, more likely to have a family history of ovarian cancer, and less likely to use oral contraceptives. Most studies adjusted for some of the ovarian cancer risk factors. This may reduce some of the effects of confounding, but statistical analyses cannot eliminate all the residual confounding. In addition, adjustments can only be made for factors that were measured, and most studies did not measure all the known ovarian cancer risk factors. On the basis of these differences, I conclude that there is residual confounding in the observational studies.

One study, Houghton 2014, assessed whether there are differences in ovarian cancer risk factors between women who used perineal talcum powder versus those who did not. Users were found to have a larger BMI on average, were less likely to have used oral contraceptives, and were less likely to have had a hysterectomy. They were also slightly more likely to be nulliparous than controls, but this did not significantly differ between the groups. These findings indicate that perineal talcum powder users differ from non-users in terms of risk factors associated with ovarian cancer. In other words, users were at more risk for developing ovarian cancer. This is additional evidence of confounding and it cannot be eliminated with statistical analyses.<sup>16,23</sup>

There is also evidence of inherent biases in the study design. The most compelling is recall bias. If there were no recall bias, the estimate of the association would be similar between case-control studies and cohort studies, both in terms of statistical significance and in terms of the magnitude of the association. As described above, the statistically significant association between perineal/genital talcum powder use and ovarian cancer seen across case-control studies is 1.25 or higher, whereas the cohort studies have values less than 1.10, which were not statistically significant. The reason that cohort studies provide a higher level of evidence is because they eliminate recall bias. Another source of bias is the way cases and controls were obtained. None of the case-control studies had a 100% participation rate. Some studies reported non-participation rates of 30% or higher.<sup>5,14,62</sup> No study provided a comparison of women who chose to participate and those who did not. Cases who had died prior to being

approached to participate in the study may have differed from controls in relevant ways. Specifically, cases who lived longer (enabling them to become part of the study) may have been healthier, which would influence lifestyle choices such as personal hygiene. It is known that controls who choose to participate in studies versus those who are eligible but do not choose to participate are generally healthier. Hence, the controls were likely to have fewer ovarian cancer risk factors than cases, which is what has been observed.

There is clear evidence of residual confounding and biases in the observational studies. Given the relatively weak association that has been observed between perineal/genital talcum powder use and ovarian cancer in some of the case-control studies, it is likely the association is spurious since residual confounding and biases exist. In order to conclude the relationship is causal, there would need to be definitive biological evidence that perineal/genital talcum powder exposure causes ovarian cancer.

### 8.3 NEW INFORMATION SINCE IARC 2010 REPORT

Several studies have been published since the IARC 2010 report,<sup>2</sup> raising the question whether IARC would make different findings today based on the new information that has become available since the time of the report. There have been several studies that have subsequently been published, including two additional cohort studies (Houghton 2014<sup>11</sup> and Gonzales 2016<sup>13</sup>), an update on the previous report from the Nurses' Health Study (Gates 2010<sup>12</sup>), a large pooled analysis (Terry 2013<sup>20</sup>), two large case-control studies (Schildkraut 2016<sup>4</sup>, Cramer 2016<sup>5</sup>) and two meta-analyses (Berge 2018<sup>38</sup>, Penninkilampi 2018<sup>39</sup>). At the time that the report was published, it was cited that there was a statistically significant association between perineal/genital talcum powder exposure and ovarian cancer, with the magnitude of the association in the range of 1.0 to 3.9 with a pooled odds ratio of 1.35. About half of the case-control studies had statistically significant associations, and for half the associations were not statistically significant.<sup>37</sup> It was also found that the single cohort study then available (Nurses' Health Study) did not observe a statistically significant association. In a subsequent published manuscript, a subset of the authors of the IARC report stated that the cohort study was "...arguably the strongest study because of its partly prospective ascertainment of exposure..."<sup>37</sup> The results regarding the dose-response relationship were reported as mixed. There was no significant dose response observed in the cohort study and positive dose-response relationship trends in two of the seven most informative case-control studies. In other case-control studies, "a non-significant, weakly positive trend was observed for either duration or frequency of use, but not for both. In the other three case-control studies, no consistent trend was observed, and the strongest associations tended to be seen among shorter-term or less frequent talc users."<sup>2</sup>

Since the IARC report, there have been two recent meta-analyses (Berge 2018 and Penninkilampi 2018) that included all the studies reported to date. These studies report the

magnitude of the association between perineal/genital talcum powder exposure and ovarian cancer as between 1.22 and 1.31, and these associations were statistically significant. This is in line with what was observed at the time of the IARC report, with perhaps a slight decrease in the association level since the pooled analysis at that time had an odds ratio of 1.35. Hence, the new meta-analyses do not substantially change the observed association in terms of either significance or magnitude. However, there have been two additional cohort studies (Women's Health Initiative and Sister Study) as well as updated results of the Nurses' Health Study. None of the cohort studies found a statistically significant association between perineal/genital talcum powder exposure and ovarian cancer. The two most recent cohort studies are consistent with what was observed in the Nurses' Health Study that was available at the time of the IARC report. In a meta-analysis of the cohort study results, Berge 2018 reports an association of 1.02 (95% CI: 0.85 to 1.20) and Penninkilampi 2018 reports an association of 1.06 (0.90 to 1.25). The additional information since the IARC report is the replication and consistency of the association observed within the initial cohort study: very small magnitude of association that is not statistically significant.

Recently, there has also been another meta-analysis, conducted by Taher et al., that has not been published yet.<sup>66</sup> These investigators report an overall odds ratio between perineal use of talcum powder and ovarian cancer of 1.28 (95% CI: 1.20 to 1.37). There was a significant association for the case-control studies (OR = 1.32; 95% CI: 1.24 to 1.4) and a non-significant association for the cohort studies (OR = 1.06; 95% CI: 0.9 to 1.25). Furthermore, they report a significant association only for the population-based case-control studies (OR = 1.34; 95% CI: 1.27 to 1.41), but not for hospital-based controls (OR = 0.96; 95% CI: 0.78 to 1.17). These results align with all the previous meta-analyses with little new information. These authors conclude, "Perineal use of talc powder is a possible cause of human ovarian cancer." Based on my years as a journal editor, I would not be surprised if they were asked to rephrase this conclusion to remove the phrase "a possible cause." Both of the most recent peer-reviewed and published meta-analyses (Penninkilampi et al.<sup>39</sup> and Berge et al.<sup>38</sup>) did not conclude that perineal talc powder use is a possible cause of human ovarian cancer based on the same information that was available to Taher et al.

There is additional information available regarding the potential dose-response relationship. The two recent, large case-control studies report a statistically significant dose-response relationship. Cramer 2016 only reports it for the frequency measure, but it is not observed for the duration or total applications. On the other hand, the Schildkraut 2016 study reports significant dose-response relationships for all three measures. There are a couple of issues with these findings. One is that the proper statistical test to establish whether the observed relationship is statistically significant has not been performed. Specifically, the test for trend includes individuals who were never exposed to talcum powder. In order to be scientifically

rigorous in determining whether there is a dose-response relationship, the test for trend should only be conducted among the individuals who had perineal/genital talcum powder exposure.<sup>101</sup> The larger concern is that these studies were performed after widespread publicity of court cases regarding an alleged association between talcum powder and ovarian cancer. Since these are case-control studies, it is quite likely that this resulted in additional recall bias, and Schildkraut did find much larger odds ratios for any genital talcum powder use and ovarian cancer for individuals interviewed after 2014.<sup>4</sup> The pooled analysis of case-control studies performed in the Terry 2013 study did not find a statistically significant dose-response relationship, and this analysis was based on results prior to increased publicity regarding lawsuits alleging that perineal talc use causes ovarian cancer. There is also additional information regarding dose-response relationship from a prospective cohort study. The result from the Nurses' Health Study that indicated a lack of a significant dose-response relationship was reproduced in the Women's Health Study. In fact, it was found that women who used perineal talcum powder for a longer duration had a numerically smaller association: 1.09 (95% CI: 0.88, 1.36) for nine or less years of use compared to 1.02 (95% CI: 0.80, 1.30) for 10 or more years of use, and there was no association for 20 years or greater use either.<sup>11</sup> It is likely that there is no statistical difference between these two associations. Finally, the two recent meta-analyses<sup>38,39</sup> did not demonstrate a consistent dose-response relationship because the doses were dichotomized and the lowest group contained never users. The unpublished Taher et al. meta-analysis performed a dose-response analysis. The results did not show a dose response when analyzed as frequency of use or for duration of use. For duration of use, it was found that if the use was between 10 and 20 years, the odds ratio was 1.42 (95% CI: 1.02 to 1.99) compared to an odds ratio of 1.19 (95% CI: 0.71 to 1.98) for 20 or more years of use. Hence, there is no compelling new information in support of a dose-response relationship. The results remain mixed and the recent case-control studies are likely further biased due to the publicity of the alleged association between talcum powder use and ovarian cancer. The cohort studies, which provide a stronger level of evidence, do not observe a dose-response relationship.

Overall, the most compelling new information provided by epidemiology studies since the IARC report is the addition of the two prospective cohort studies. These studies confirm what was observed in the cohort study that was available at the time of the IARC report: the lack of a statistically significant association between perineal/genital talcum powder use and the lack of a dose-response relationship. Likewise, the case-control studies and their meta-analyses continue to observe a significant association. However, the new studies, like the old, suffer from recall biases and selection biases. There is evidence that recall bias is compounded in the most recent Schildkraut case-control study due to the publicity regarding the alleged association between talcum powder and ovarian cancer. If there is no new compelling biological evidence that perineal application of talcum powder causes ovarian cancer, the current data remain consistent with the original IARC ruling.

## 9 CONCLUSION

It is my professional opinion that there is no evidence of a causal relationship between perineal/genital talcum powder exposure and ovarian cancer. This is based on my extensive and rigorous review of the epidemiology studies (and to a lesser extent, my review of scientific literature) and my experience and expertise in assessing studies for the level of evidence in the data. It is known that relatively weak associations are likely spurious due to residual confounding and biases, which I find to be the case here. There is evidence of recall bias and/or patient selection bias in the case-control studies because the cohort studies do not replicate the magnitude or statistical significance of the association. There is no consistent evidence of a dose-response relationship among the case-control studies and lack of evidence for a dose-response relationship in the cohort studies. Cohort studies provide stronger evidence than do case-control studies. There is evidence of residual confounding in the observational studies because ovarian cancer cases differ from controls on a host of ovarian cancer risk factors, in addition to the exposure to perineal/genital talcum exposure. Finally, there does not appear to be compelling and definitive evidence from cell line experiments, animal models and translational studies that support biological plausibility or a biological mechanism. On the basis of this, there is a lack of evidence to support a causal relationship.

My opinions are made to a reasonable degree of scientific certainty. I reserve the right to supplement or change my opinion as new information becomes available.

## 10 REFERENCES

1. Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med*. 1965;58:295-300.
2. IARC. *IARC Monographs on the evaluation of carcinogenic risk to humans: carbon black, titanium dioxide, and talc*. Lyon: International Agency for Research on Cancer;2010.
3. Ness RB, Grisso JA, Cottreau C, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology*. 2000;11(2):111-117.
4. Schildkraut JM, Abbott SE, Alberg AJ, et al. Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES). *Cancer Epidemiol Biomarkers Prev*. 2016;25(10):1411-1417.
5. Cramer DW, Vitonis AF, Terry KL, Welch WR, Titus LJ. The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States. *Epidemiology*. 2016;27(3):334-346.
6. Stadel BV, Rubin GL, Webster LA, Schlesselman JJ, Wingo PA. Oral contraceptives and breast cancer in young women. *Lancet*. 1985;2(8462):970-973.
7. Schlesselman J. *Case-control studies: design, conduct, analysis*. New York, NY: Oxford University Press; 1982.
8. Lindefors-Harris BM, Eklund G, Adami HO, Meirik O. Response bias in a case-control study: analysis utilizing comparative data concerning legal abortions from two independent Swedish studies. *Am J Epidemiol*. 1991;134(9):1003-1008.
9. Schulz KF, Grimes DA. Case-control studies: research in reverse. *Lancet*. 2002;359(9304):431-434.
10. Gertig DM, Hunter DJ, Cramer DW, et al. Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst*. 2000;92(3):249-252.
11. Houghton SC, Reeves KW, Hankinson SE, et al. Perineal powder use and risk of ovarian cancer. *J Natl Cancer Inst*. 2014;106(9).
12. Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk factors for epithelial ovarian cancer by histologic subtype. *Am J Epidemiol*. 2010;171(1):45-53.
13. Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR. Douching, Talc Use, and Risk of Ovarian Cancer. *Epidemiology*. 2016;27(6):797-802.
14. Wu AH, Pearce CL, Tseng CC, Pike MC. African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. *Cancer Epidemiol Biomarkers Prev*. 2015;24(7):1094-1100.
15. McTiernan A. Expert Report. *MDL No 16-2738 (FLW) (LHG)*. Vol 262018.
16. Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. *BMJ*. 1998;316(7125):140-144.
17. Meinert CL. Meta-analysis: science or religion? *Control Clin Trials*. 1989;10(4 Suppl):257S-263S.
18. Bialer JC, 3rd. The practice of meta-analysis. *J Clin Epidemiol*. 1995;48(1):149-157.
19. Feinstein AR. Meta-analysis: statistical alchemy for the 21st century. *J Clin Epidemiol*. 1995;48(1):71-79.
20. Terry KL, Karageorgi S, Shvetsov YB, et al. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res (Phila)*. 2013;6(8):811-821.
21. LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med*. 1997;337(8):536-542.
22. Stegenga J. Is meta-analysis the platinum standard of evidence? *Stud Hist Philos Biol Biomed Sci*. 2011;42(4):497-507.
23. Egger M, Ebrahim S, Smith GD. Where now for meta-analysis? *Int J Epidemiol*. 2002;31(1):1-5.
24. Ioannidis JP, Haidich AB, Pappa M, et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. *JAMA*. 2001;286(7):821-830.
25. Smith GD, Phillips AN, Neaton JD. Smoking as "independent" risk factor for suicide: illustration of an artifact from observational epidemiology? *Lancet*. 1992;340(8821):709-712.
26. Boyd NF, Martin LJ, Noffel M, Lockwood GA, Trichler DL. A meta-analysis of studies of dietary fat and breast cancer risk. *Br J Cancer*. 1993;68(3):627-636.
27. Hunter DJ, Spiegelman D, Adami HO, et al. Cohort studies of fat intake and the risk of breast cancer--a pooled analysis. *N Engl J Med*. 1996;334(6):356-361.

28. Jha P, Flather M, Lonn E, Farkouh M, Yusuf S. The antioxidant vitamins and cardiovascular disease. A critical review of epidemiologic and clinical trial data. *Ann Intern Med.* 1995;123(11):860-872.
29. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg.* 2011;128(1):305-310.
30. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet.* 2002;359(9302):248-252.
31. Boffetta P. Causation in the Presence of Weak Associations. *Crit Rev Food Sci.* 2010;50:13-16.
32. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol.* 2015;12:14.
33. Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. *Obstet Gynecol.* 1992;80(1):19-26.
34. Gross AJ, Berg PH. A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer. *J Expo Anal Environ Epidemiol.* 1995;5(2):181-195.
35. Cramer DW, Liberman RF, Titus-Ernstoff L, et al. Genital talc exposure and risk of ovarian cancer. *Int J Cancer.* 1999;81(3):351-356.
36. Huncharek M, Geschwind JF, Kupelnick B. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. *Anticancer Res.* 2003;23(2C):1955-1960.
37. Langseth H, Hankinson SE, Siemiatycki J, Weiderpass E. Perineal use of talc and risk of ovarian cancer. *J Epidemiol Community Health.* 2008;62(4):358-360.
38. Berge W, Mundt K, Luu H, Boffetta P. Genital use of talc and risk of ovarian cancer: a meta-analysis. *Eur J Cancer Prev.* 2018;27(3):248-257.
39. Penninkilampi R, Eslick GD. Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. *Epidemiology.* 2018;29(1):41-49.
40. Huncharek M, Muscat J, Onitilo A, Kupelnick B. Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies. *Eur J Cancer Prev.* 2007;16(5):422-429.
41. Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: a case-control study. *Cancer.* 1982;50(2):372-376.
42. Hartge P, Hoover R, Leshner LP, McGowan L. Talc and ovarian cancer. *JAMA.* 1983;250(14):1844.
43. Whittemore AS, Wu ML, Paffenbarger RS, Jr., et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am J Epidemiol.* 1988;128(6):1228-1240.
44. Harlow BL, Weiss NS. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *Am J Epidemiol.* 1989;130(2):390-394.
45. Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. *Br J Cancer.* 1989;60(4):592-598.
46. Rosenblatt KA, Szklo M, Rosenshein NB. Mineral fiber exposure and the development of ovarian cancer. *Gynecol Oncol.* 1992;45(1):20-25.
47. Chen Y, Wu PC, Lang JH, Ge WJ, Hartge P, Brinton LA. Risk factors for epithelial ovarian cancer in Beijing, China. *Int J Epidemiol.* 1992;21(1):23-29.
48. Tzonou A, Polychronopoulou A, Hsieh CC, Rebelakos A, Karakatsani A, Trichopoulos D. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int J Cancer.* 1993;55(3):408-410.
49. Purdie D, Green A, Bain C, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. *Int J Cancer.* 1995;62(6):678-684.
50. Shushan A, Paltiel O, Gordon L, Schenker JG. Ovarian cancer of low malignant potential is not associated with positive familial history. *Am J Obstet Gynecol.* 1996;175(2):507-508.
51. Chang S, Risch HA. Perineal talc exposure and risk of ovarian carcinoma. *Cancer.* 1997;79(12):2396-2401.
52. Cook LS, Kamb ML, Weiss NS. Perineal powder exposure and the risk of ovarian cancer. *Am J Epidemiol.* 1997;145(5):459-465.
53. Green A, Purdie D, Bain C, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. *Int J Cancer.* 1997;71(6):948-951.

54. Godard B, Foulkes WD, Provencher D, et al. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *Am J Obstet Gynecol*. 1998;179(2):403-410.
55. Wong C, Hempling RE, Piver MS, Natarajan N, Mettlin CJ. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstet Gynecol*. 1999;93(3):372-376.
56. Pike MC, Pearce CL, Peters R, Cozen W, Wan P, Wu AH. Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study. *Fertil Steril*. 2004;82(1):186-195.
57. Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *Int J Cancer*. 2004;112(3):458-464.
58. Goodman MT, Lurie G, Thompson PJ, McDuffie KE, Carney ME. Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk. *Endocr Relat Cancer*. 2008;15(4):1055-1060.
59. Merritt MA, Green AC, Nagle CM, Webb PM, Australian Cancer S, Australian Ovarian Cancer Study G. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer*. 2008;122(1):170-176.
60. Moorman PG, Palmieri RT, Akushevich L, Berchuck A, Schildkraut JM. Ovarian cancer risk factors in African-American and white women. *Am J Epidemiol*. 2009;170(5):598-606.
61. Wu AH, Pearce CL, Tseng CC, Templeman C, Pike MC. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *Int J Cancer*. 2009;124(6):1409-1415.
62. Rosenblatt KA, Weiss NS, Cushing-Haugen KL, Wicklund KG, Rossing MA. Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes Control*. 2011;22(5):737-742.
63. Kurta ML, Moysich KB, Weissfeld JL, et al. Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2012;21(8):1282-1292.
64. Lo-Ciganic WH, Zgibor JC, Bunker CH, Moysich KB, Edwards RP, Ness RB. Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer. *Epidemiology*. 2012;23(2):311-319.
65. Gates MA, Tworoger SS, Terry KL, et al. Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2008;17(9):2436-2444.
66. Taher MK, Farhat N, Karyakina N, et al. Systematic review and meta-analysis of the association between perineal use of talc and risk of ovarian cancer. (unpublished).
67. Taubes G. Epidemiology faces its limits. *Science*. 1995;269(5221):164-169.
68. Wynder EL. Guidelines to the Epidemiology of Weak Associations - Epilogue. *Prev Med*. 1987;16(2):211-212.
69. Moorman P. Expert report. *MLD No. 16-2738 (FLW) (LHG)*. Vol 262018.
70. Smith-Bindman R. Expert Report. *MDL No. 16-2738 (FLW) (LHG)*. Vol 262018.
71. Wolf J. Expert Report. *MDL No. 16-2738 (FLW) (LHG)*. Vol 262018.
72. Narod SA. Talc and ovarian cancer. *Gynecol Oncol*. 2016;141(3):410-412.
73. Moorman P. Expert Report. *MDL No. 16-2738 (FLW) (LHG)*. Vol 262018.
74. Siemiatycki J. Expert Report. *MDL No. 16-2738 (FLW) (LHG)*. Vol 262018.
75. Cumming G. Inference by eye: reading the overlap of independent confidence intervals. *Stat Med*. 2009;28(2):205-220.
76. Zambelli-Weiner A. Expert Report. *MLD No. 16-2738 (FLW) (LHG)*. Vol 262018.
77. Heller DS, Westhoff C, Gordon RE, Katz N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Am J Obstet Gynecol*. 1996;174(5):1507-1510.
78. Rasmussen CB, Kjaer SK, Albieri V, et al. Pelvic Inflammatory Disease and the Risk of Ovarian Cancer and Borderline Ovarian Tumors: A Pooled Analysis of 13 Case-Control Studies. *Am J Epidemiol*. 2017;185(1):8-20.
79. Zhou Z, Zeng F, Yuan J, et al. Pelvic inflammatory disease and the risk of ovarian cancer: a meta-analysis. *Cancer Causes Control*. 2017;28(5):415-428.
80. Baandrup L, Faber MT, Christensen J, et al. Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. *Acta Obstet Gynecol Scand*. 2013;92(3):245-255.
81. Bonovas S, Filioussi K, Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. *Br J Clin Pharmacol*. 2005;60(2):194-203.

82. Ni X, Ma J, Zhao Y, Wang Y, Wang S. Meta-analysis on the association between non-steroidal anti-inflammatory drug use and ovarian cancer. *Br J Clin Pharmacol*. 2013;75(1):26-35.
83. Trabert B, Ness RB, Lo-Ciganic WH, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. *J Natl Cancer Inst*. 2014;106(2):djt431.
84. Trabert B, Poole EM, White E, et al. Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium. *J Natl Cancer Inst*. 2019;111(2):137-145.
85. Saed G. The videotaped deposition of Saed Ghassen, Ph.D. 2019.
86. Coggiola M, Bosio D, Pira E, et al. An update of a mortality study of talc miners and millers in Italy. *Am J Ind Med*. 2003;44(1):63-69.
87. Wild P, Leodolter K, Refregier M, Schmidt H, Zidek T, Haidinger G. A cohort mortality and nested case-control study of French and Austrian talc workers. *Occup Environ Med*. 2002;59(2):98-105.
88. Wergeland E, Andersen A, Baerheim A. Morbidity and mortality in talc-exposed workers. *Am J Ind Med*. 1990;17(4):505-513.
89. Stallones RA. The use and abuse of subgroup analysis in epidemiological research. *Prev Med*. 1987;16(2):183-194.
90. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine--reporting of subgroup analyses in clinical trials. *N Engl J Med*. 2007;357(21):2189-2194.
91. Egger M, Smith GD, Altman DG. *Systematic reviews in health care : meta-analysis in context*. 2nd ed. London: BMJ; 2001.
92. Vandembroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology*. 2007;18(6):805-835.
93. Kerr NL. HARKing: hypothesizing after the results are known. *Pers Soc Psychol Rev*. 1998;2(3):196-217.
94. Smith-Bindman R. Videotaped deposition of Rebecca Smith-Bindman, M.D.; Volume I. In: Zellers MC, ed2019.
95. Smith-Bindman R. Videotaped deposition of Rebecca Smith-Bindman, M.D., Volume II. In: Zellers MC, ed2019.
96. Bland JM, Altman DG. Statistics notes. The odds ratio. *BMJ*. 2000;320(7247):1468.
97. Hall J, Smith-Bindman R. TalcDataResults-janehall.xlsx. 2018.
98. Hunn J, Rodriguez GC. Ovarian cancer: etiology, risk factors, and epidemiology. *Clin Obstet Gynecol*. 2012;55(1):3-23.
99. Lahmann PH, Cust AE, Friedenreich CM, et al. Anthropometric measures and epithelial ovarian cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*. 2010;126(10):2404-2415.
100. Faber MT, Jensen A, Frederiksen K, et al. Oral contraceptive use and impact of cumulative intake of estrogen and progestin on risk of ovarian cancer. *Cancer Causes Control*. 2013;24(12):2197-2206.
101. Maclure M, Greenland S. Tests for trend and dose response: misinterpretations and alternatives. *Am J Epidemiol*. 1992;135(1):96-104.

# Materials Reviewed and Considered

1. Baandrup et al., Nonsteroidal Anti-Inflammatory Drugs and Risk of Ovarian Cancer: Systematic Review and Meta-Analysis of Observational Studies, 92(3) Acta Obstet Gynecol Scand. 245 (2013)
2. Bailer JC, III. The practice of meta-analysis. J Clin Epidemiol. 1995;48(1):149-157.
3. Berge W, Mundt K, Luu H, Boffetta P. Genital use of talc and risk of ovarian cancer: a meta-analysis. Eur J Cancer Prev. 2018;27(3):248-257.
4. Bland JM, Altman DG. Statistics notes. The odds ratio. BMJ. 2000;320(7247):1468.
5. Boffetta P. Causation in the presence of weak associations. Crit Rev Food Sci and Nut. 2010;50:13-16.
6. Bonovas et al., Do Nonsteroidal Anti-Inflammatory Drugs Affect the Risk of Developing Ovarian Cancer? A Meta-Analysis, 60 Brit. J. Clinical Pharmacology 194 (2005)
7. Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. Br J Cancer. 1989;60(4):592-598.
8. Boyd NF, Martin LJ, Noffel M, Lockwood GA, Trichler DL. A meta-analysis of studies of dietary fat and breast cancer risk. Br J Cancer. 1993;68(3):627-636.
9. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg. 2011;128(1):305-310.
10. Chang S, Risch HA. Perineal talc exposure and risk of ovarian carcinoma. Cancer. 1997;79(12):2396-2401.
11. Chen Y, Wu PC, Lang JH, Ge WJ, Hartge P, Brinton LA. Risk factors for epithelial ovarian cancer in Beijing, China. Int J Epidemiol. 1992;21(1):23-29.
12. Coggiola M, Bosio D, Pira E, et al. An update of a mortality study of talc miners and millers in Italy. Am J Ind Med. 2003;44(1):63-69.
13. Cook LS, Kamb ML, Weiss NS. Perineal powder exposure and the risk of ovarian cancer. Am J Epidemiol. 1997;145(5):459-465.
14. Cramer DW, Liberman RF, Titus-Ernstoff L, et al. Genital talc exposure and risk of ovarian cancer. Int J Cancer. 1999;81(3):351-356.
15. Cramer DW, Vitonis AF, Terry KL, Welch WR, Titus LJ. The association between talc use and ovarian cancer: A retrospective case-control study in two US states. Epidemiology. 2016;27(3):334-346.
16. Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: a case-control study. Cancer. 1982;50(2):372-376.
17. Cumming G. Inference by eye: reading the overlap of independent confidence intervals. Stat Med. 2009;28(2):205-220.
18. Egger M, Ebrahim S, Smith GD. Where now for meta-analysis? Int J Epidemiol. 2002;31(1):1-5.
19. Egger M, Schneider M, Davey Smith G. Spurious precision? Meta-analysis of observational studies. BMJ. 1998;316(7125):140-144.
20. Egger M, Smith GD, Altman DG. Systematic reviews in health care: meta-analysis in context. 2nd ed. London: BMJ; 2001.

21. Faber MT, Jensen A, Frederiksen K, et al. Oral contraceptive use and impact of cumulative intake of estrogen and progestin on risk of ovarian cancer. *Cancer Causes Control*. 2013;24(12):2197-2206.
22. Fedak KM, Bernal A, Capshaw ZA, Gross S. Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerg Themes Epidemiol*. 2015;12:14:1-9.
23. Feinstein AR. Meta-analysis: statistical alchemy for the 21st century. *J Clin Epidemiol*. 1995;48(1):71-79.
24. Finkelstein MM. Malignant mesothelioma incidence among talc miners and millers in New York State. *Am J Ind Med*. 2012;55(10):863-868.
25. Finkelstein, Re Mortality of Talc Miners and Millers From Val Chisone, Northern Italy (Letter to the Editor), 59(10) *JOEM* e194 (2017)
26. Finley BL, Benson SM, Marsh GM. Cosmetic talc as a risk factor for pleural mesothelioma: a weight of evidence evaluation of the epidemiology. *Inhal Toxicol*. 2017;29(4):179-185.
27. Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk factors for epithelial ovarian cancer by histologic subtype. *Am J Epidemiol*. 2010;171(1):45-53.
28. Gates MA, Tworoger SS, Terry KL, et al. Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2008;17(9):2436-2444.
29. Gertig DM, Hunter DJ, Cramer DW, et al. Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst*. 2000;92(3):249-252.
30. Godard B, Foulkes WD, Provencher D, et al. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *Am J Obstet Gynecol*. 1998;179(2):403-410.
31. Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR. Douching, talc use, and risk of ovarian cancer. *Epidemiology*. 2016;27(6):797-802.
32. Goodman MT, Lurie G, Thompson PJ, McDuffie KE, Carney ME. Association of two common single-nucleotide polymorphisms in the CYP19A1 locus and ovarian cancer risk. *Endocr Relat Cancer*. 2008;15(4):1055-1060.
33. Green A, Purdie D, Bain C, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. *Int J Cancer*. 1997;71(6):948-951.
34. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet*. 2002;359(9302):248-252.
35. Gross AJ, Berg PH. A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer. *J Expo Anal Environ Epidemiol*. 1995;5(2):181-195.
36. Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. *Obstet Gynecol*. 1992;80(1):19-26.
37. Harlow BL, Weiss NS. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *Am J Epidemiol*. 1989;130(2):390-394.
38. Hartge P, Hoover R, Leshner LP, McGowan L. Talc and ovarian cancer. *JAMA*. 1983;250(14):1844.

39. Heller DS, Westhoff C, Gordon RE, Katz N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Am J Obstet Gynecol.* 1996;174(5):1507-1510.
40. Hill AB. The environment and disease: association or causation? *Proc R Soc Med.* 1965;58:295-300.
41. Houghton SC, Reeves KW, Hankinson SE, et al. Perineal powder use and risk of ovarian cancer. *J Natl Cancer Inst.* 2014;106(9): 1-6.
42. Huncharek M, Geschwind JF, Kupelnick B. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. *Anticancer Res.* 2003;23(2C):1955-1960.
43. Huncharek M, Muscat J, Onitilo A, Kupelnick B. Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies. *Eur J Cancer Prev.* 2007;16(5):422-429.
44. Hunn J, Rodriguez GC. Ovarian cancer: etiology, risk factors, and epidemiology. *Clin Obstet Gynecol.* 2012;55(1):3-23.
45. Hunter DJ, Spiegelman D, Adami HO, et al. Cohort studies of fat intake and the risk of breast cancer--a pooled analysis. *N Engl J Med.* 1996;334(6):356-361.
46. International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risk to humans: carbon black, titanium dioxide, and talc. Lyon: International Agency for Research on Cancer;2010.
47. Ioannidis JP, Haidich AB, Pappa M, et al. Comparison of evidence of treatment effects in randomized and nonrandomized studies. *JAMA.* 2001;286(7):821-830.
48. Jan. 24, 2019 Production of Materials for the Deposition of Rebecca Smith-Bindman, M.D. (MDL No. 2738)
49. Jha P, Flather M, Lonn E, Farkouh M, Yusuf S. The antioxidant vitamins and cardiovascular disease. A critical review of epidemiologic and clinical trial data. *Ann Intern Med.* 1995;123(11):860-872.
50. Jordan SJ, Green AC, Whiteman DC, Webb PM. Risk factors for benign serous and mucinous epithelial ovarian tumors. *Obstet Gynecol.* 2007;109(3):647-654.
51. Kane S. Expert Report. MDL No. 16-2738 (FLW (LHG). Vol 262018.
52. Kane S. Videotaped deposition of Sarah Kane, M.D., In: Ahern HK, ed2019.
53. Kerr NL. HARKing: hypothesizing after the results are known. *Pers Soc Psychol Rev.* 1998;2(3):196-217.
54. Kleinfeld M, Messite J, Kooyman O, Zaki MH. Mortality among talc miners and millers in New York State. *Arch Environ Health.* 1967;14(5):663-667.
55. Kurta ML, Moysich KB, Weissfeld JL, et al. Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. *Cancer Epidemiol Biomarkers Prev.* 2012;21(8):1282-1292.
56. Lahmann PH, Cust AE, Friedenreich CM, et al. Anthropometric measures and epithelial ovarian cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer.* 2010;126(10):2404-2415.
57. Langseth H, Hankinson SE, Siemiatycki J, Weiderpass E. Perineal use of talc and risk of ovarian cancer. *J Epidemiol Community Health.* 2008;62(4):358-360.

58. LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med.* 1997;337(8):536-542.
59. Lindefors-Harris BM, Eklund G, Adami HO, Meirik O. Response bias in a case-control study: analysis utilizing comparative data concerning legal abortions from two independent Swedish studies. *Am J Epidemiol.* 1991;134(9):1003-1008.
60. Lo-Ciganic WH, Zgibor JC, Bunker CH, Moysich KB, Edwards RP, Ness RB. Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer. *Epidemiology.* 2012;23(2):311-319.
61. Maclure M, Greenland S. Tests for trend and dose response: misinterpretations and alternatives. *Am J Epidemiol.* 1992;135(1):96-104.
62. McTiernan A. Expert Report. MDL No 16-2738 (FLW) (LHG). Vol 262018.
63. McTiernan A. Videotaped deposition of Anne McTiernan, Ph.D., In: Williams BH, ed2019.
64. Meinert CL. Meta-analysis: science or religion? *Control Clin Trials.* 1989;10(4 Suppl):257S-263S.
65. Merritt et al., Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int. J. Cancer* (2008) 122:170-76
66. Merritt MA, Green AC, Nagle CM, Webb PM, Australian Cancer Study, Australian Ovarian Cancer Study Group. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer.* 2008;122(1):170-176.
67. Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *Int J Cancer.* 2004;112(3):458-464.
68. Moorman P. Expert Report. MDL No. 16-2738 (FLW) (LHG). Vol 262018.
69. Moorman PG, Palmieri RT, Akushevich L, Berchuck A, Schildkraut JM. Ovarian cancer risk factors in African-American and white women. *Am J Epidemiol.* 2009;170(5):598-606.
70. Moorman P. Videotaped deposition of Patricia Moorman, M.S.P.H., Ph.D., In: James SA, ed2019.
71. Ness RB, Grisso JA, Cottreau C, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology.* 2000;11(2):111-117.
72. Ni et al., Meta-Analysis on the Association Between Non-Steroidal Anti-Inflammatory Drug Use and Ovarian Cancer, 75(1) *Brit. J. Clinical Pharmacology* 26 (2012)
73. Penninkilampi R, Eslick GD. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. *Epidemiology.* 2018;29(1):41-49.
74. Pike MC, Pearce CL, Peters R, Cozen W, Wan P, Wu AH. Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study. *Fertil Steril.* 2004;82(1):186-195.
75. Pira E, Coggiola M, Ciocan C, et al. Mortality of talc miners and millers From Val Chisone, Northern Italy: an updated cohort study. *J Occup Environ Med.* 2017;59(7):659-664.

76. Purdie D, Green A, Bain C, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. *Int J Cancer*. 1995;62(6):678-684.
77. Rasmussen, CB, et al. Is pelvic inflammatory disease a risk factor for ovarian cancer? *Cancer Epidemiol Biomarkers Prev* 2017; 26(1): 104-109
78. Rosenblatt KA, Szklo M, Rosenshein NB. Mineral fiber exposure and the development of ovarian cancer. *Gynecol Oncol*. 1992;45(1):20-25.
79. Rosenblatt KA, Weiss NS, Cushing-Haugen KL, Wicklund KG, Rossing MA. Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes Control*. 2011;22(5):737-742.
80. Rubino et al., Mortality and Morbidity Among Talc Miners and Millers in Italy, in DUSTS AND DISEASE (Lemen & Dement eds., 1979)
81. Rubino et al., Mortality Study of Talc Miners and Millers, 18(3) *J Occupational Med* 186 (1976)
82. Saed G. Expert Report. MDL No. 16-2738 (FLW (LHG)). Vol 262018.
83. Saed G. Videotaped deposition of Ghassan Saed, Ph.D., Volume I. In: Hegarty MC, ed2019.
84. Saed G. Videotaped deposition of Ghassan Saed, Ph.D., Volume II. In: Hegarty MC, ed2019.
85. Schildkraut JM, Abbott SE, Alberg AJ, et al. Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiol Biomarkers Prev*. 2016;25(10):1411-1417.
86. Schlesselman J. Case-control studies: design, conduct, analysis. New York, NY: Oxford University Press. 1982.
87. Schulz KF, Grimes DA. Case-control studies: research in reverse. *Lancet*. 2002;359(9304):431-434.
88. Selevan SG, Dement JM, Wagoner JK, Froines JR. Mortality patterns among miners and millers of non-asbestiform talc: preliminary report. *J Environ Pathol Toxicol*. 1979;2(5):273-284.
89. Shushan A, Paltiel O, Gordon L, Schenker JG. Ovarian cancer of low malignant potential is not associated with positive familial history. *Am J Obstet Gynecol*. 1996;175(2):507-508.
90. Siemiatycki J. Expert Report. MDL No. 16-2738 (FLW) (LHG). Vol 262018.
91. Siemiatycki J. Videotaped deposition of Jack Siemiatycki, Ph.D., In: Branscome KO, ed2019.
92. Singh S. Expert Report. MDL No. 16-2738 (FLW (LHG)). Vol 262018.
93. Singh S. Videotaped deposition of Sonal Singh, M.D., In: Zellers MC, ed2019.
94. Smith GD, Phillips AN, Neaton JD. Smoking as "independent" risk factor for suicide: illustration of an artifact from observational epidemiology? *Lancet*. 1992;340(8821):709-712.
95. Smith-Bindman R. Expert Report. MDL No. 16-2738 (FLW) (LHG). Vol 262018.
96. Smith-Bindman R. Videotaped deposition of Rebecca Smith-Bindman, M.D., Volume I. In: Zellers MC, ed2019.

97. Smith-Bindman R. Videotaped deposition of Rebecca Smith-Bindman, M.D., Volume II. In: Zellers MC, ed2019.
98. Stadel BV, Rubin GL, Webster LA, Schlesselman JJ, Wingo PA. Oral contraceptives and breast cancer in young women. *Lancet*. 1985;2(8462):970-973.
99. Stallones RA. The use and abuse of subgroup analysis in epidemiological research. *Prev Med*. 1987;16(2):183-194.
100. Stegenga J. Is meta-analysis the platinum standard of evidence? *Stud Hist Philos Biol Biomed Sci*. 2011;42(4):497-507.
101. Taher MK, Farhat N, Karyakina N, et al. Systematic review and meta-analysis of the association between perineal use of talc and risk of ovarian cancer. (unpublished).
102. Taubes G. Epidemiology faces its limits. *Science*. 1995;269(5221):164-169.
103. Terry KL, Karageorgi S, Shvetsov YB, et al. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res (Phila)*. 2013;6(8):811-821.
104. Trabert et al., Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium, *J. Nat'l Cancer Inst.* (2019) 111(2):137-145, 139-42
105. Trabert et al., Aspirin, Nonaspirin Nonsteroidal Anti-inflammatory Drug, and Acetaminophen Use and Risk of Invasive Epithelial Ovarian Cancer: A Pooled Analysis in the Ovarian Cancer Association Consortium, 106(2) *J. Nat'l Cancer Inst.* 1, 5 (2014)
106. Tzonou A, Polychronopoulou A, Hsieh CC, Rebelakos A, Karakatsani A, Trichopoulos D. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int J Cancer*. 1993;55(3):408-410.
107. Vandembroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology*. 2007;18(6):805-835.
108. Wang R, Lagakos SW, Ware JH, Hunter DJ, Drazen JM. Statistics in medicine--reporting of subgroup analyses in clinical trials. *N Engl J Med*. 2007;357(21):2189-2194.
109. Whittemore AS, Wu ML, Paffenbarger RS, Jr., et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am J Epidemiol*. 1988;128(6):1228-1240.
110. Wolf J. Expert Report. MDL No. 16-2738 (FLW) (LHG). Vol 262018.
111. Wong C, Hempling RE, Piver MS, Natarajan N, Mettlin CJ. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstet Gynecol*. 1999;93(3):372-376.
112. World Health Org., Intl. Agency Res. Cancer., IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 93 Carbon Black, Titanium Dioxide, and Talc (2010)
113. Wu AH, Pearce CL, Tseng CC, Pike MC. African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic whites after considering nongenetic risk factors and oophorectomy rates. *Cancer Epidemiol Biomarkers Prev*. 2015;24(7):1094-1100.
114. Wu AH, Pearce CL, Tseng CC, Templeman C, Pike MC. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *Int J Cancer*. 2009;124(6):1409-1415.

115. Wynder EL. Guidelines to the epidemiology of weak associations - epilogue. Preventive Medicine. 1987;16(2):211-212.
116. Zambelli-Weiner A. Expert Report. MDL No. 16-2738 (FLW) (LHG). Vol 262018.
117. Zhou Z, et al. Pelvic inflammatory disease and the risk of ovarian cancer: a meta-analysis. Cancer Causes Control 2017 May; 28(5) 415-428. Doi:10.1007/s10552-017-0873-3

# EXHIBIT A

**WEILL CORNELL MEDICAL COLLEGE CURRICULUM VITAE FORM**

(REQUIRED FORMAT)

Signature (required):	<i>Karla V. Ballman</i>
Version date:	22 February 2019

**A. GENERAL INFORMATION**

**Required Information:**

Name: First, Middle, Last	Karla V. Ballman
Office address:	Healthcare Policy and Research LA-225 Weill Cornell Medical College 402 East 67 <sup>th</sup> Street New York, NY 10065
Office telephone:	646-962-8023
Office fax:	646-962-0281
Home address:	430 East 63 <sup>rd</sup> Street Apt. 12G New York, NY 10065
Home telephone:	507-301-3013
Cell phone:	507-301-3013
Beeper:	N/A
Work Email:	<a href="mailto:kab2053@med.cornell.edu">kab2053@med.cornell.edu</a>
Personal Email:	<a href="mailto:kvballman@gmail.com">kvballman@gmail.com</a>
Citizenship:	USA
If not a U.S. Citizen, do you have:	Immigrant visa (green card)?  Non-immigrant Visa? Type:

**Optional Information (not required but helpful):**

Birth date:	11/14/1960
Birth place:	St. Cloud, MN

Marital status:	Divorced
Race/Ethnicity:	Caucasian

**B. EDUCATIONAL BACKGROUND**

1. Academic Degree(s): B.A. and higher; institution name and location; dates attended; date of award. Expand the table as needed.

Degree (abbreviation)	Institution Name and Location	Dates attended	Year Awarded
B.A.	Macalester College St. Paul, MN	9/1979 to 5/1983	1983
Scientiæ Magister (S.M.)	Massachusetts Institute of Technology Cambridge, MA	9/1985 to 6/1991	1989
Ph.D.	Massachusetts Institute of Technology Cambridge, MA	9/1985 to 6/1991	1991

2. Post-doctoral training (include residency/fellowships): In chronological order beginning with post-doctoral training positions; include full titles, ranks and inclusive dates held. Expand the tables as needed.

N/A

3. Continuing Medical Education Courses/Certificates

N/A

4. Other Educational Experiences

N/A

**C. LICENSURE, BOARD CERTIFICATION, MALPRACTICE**

1. Licensure: Every physician appointed to the Hospital staff, except interns, and aliens in the US via non-immigrant visas, must have a New York State license or a temporary certificate in lieu of the license.

N/A

2. Board Certification

N/A

3. Malpractice Insurance

N/A

**D. PROFESSIONAL POSITIONS AND EMPLOYMENT**

**1. Academic positions (teaching and research)**

Title	Institution name and location	Dates held
Assistant Professor of Mathematics and Computer Science	Macalester College St. Paul, MN	8/1991 to 6/1999
Lecturer of Statistics	University of Auckland Auckland, New Zealand	1/1994 to 7/1996
Assistant Professor of Biostatistics	Mayo Clinic College of Medicine Rochester, MN	12/1999 to 7/2001
Associate Professor of Biostatistics	Mayo Clinic College of Medicine Rochester, MN	7/2001 to 10/2007
Adjunct Associate Professor of Biostatistics	University of Minnesota Minneapolis, MN	9/2007 to 7/2015
Adjunct Associate Professor	Biomedical Informatics and Computation Biology, University of Minnesota Rochester Rochester, MN	9/2010 to 7/2015
Professor of Biostatistics	Mayo Clinic College of Medicine	11/2014 to 7/2015
Professor of Healthcare Policy and Research Tenure awarded (11/2016)	Weill Cornell Medical College New York, NY	7/2015 to present

**2. Hospital positions (e.g., attending physician)**  
**N/A**

**3. Other Employment**

Title	Institution name and location	Dates held
Actuarial Trainee	Minnesota Mutual Life Insurance Company St. Paul, MN	1983 to 1985
Consultant	AT&T Bell Labs Software Production Research Naperville, IL	1991 to 1994
Research Associate	Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic Rochester, MN	1999 to 2002
Senior Research Associate	Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic Rochester, MN	2002 to 2004
Senior Associate Consultant	Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic Rochester, MN	2004 to 2007

Senior Associate Consultant	Division of Biomedical Informatics Department of Health Sciences Research, Mayo Clinic Rochester, MN	2005 to 2007
Group Statistician	American College of Surgeons Oncology Group (ACOSOG) Statistics and Data Center Rochester, MN	2006 to 2014
Chair	Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic Rochester, MN	2006 to 2008
Consultant	Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic Rochester, MN	2007 to 2008
Consultant	Division of Biomedical Statistics and Informatics, Department of Health Sciences Research, Mayo Clinic Rochester, MN	2008 to 2015
Associate Editor	Journal of Clinical Oncology	2010 to 2017
Deputy Editor	Journal of Clinical Oncology	2017 to present
Consultant	Department of Surgery, Mayo Clinic Rochester, MN	2012 to 2015
Director of Biostatistics	Alliance Statistics and Data Center Rochester, MN	2013 to 2015
Division Chief of Biostatistics and Epidemiology	Healthcare Research and Policy Weill Cornell Medical College New York, NY	07/2015 to present

**E. EMPLOYMENT STATUS (current or anticipated)**

Name of Employer(s): Weill Cornell Medical College
Employment Status (choose one, delete the others): Full-time salaried by Weill Cornell

**F. INSTITUTIONAL/HOSPITAL AFFILIATION**

N/A

**G. PERCENT EFFORT AND INSTITUTIONAL RESPONSIBILITIES**

WCMC ANTICIPATED % EFFORT	(%)	Does the activity involve WCMC students/researchers? (Yes/No)
TEACHING	20%	yes
CLINICAL	0%	
ADMINISTRATIVE	40%	no
RESEARCH	40%	yes
TOTAL	100%	

**INSTITUTIONAL RESPONSIBILITIES**

1. Teaching (e.g., specific teaching functions, courses taught, dates: For guidance refer to Teaching Metrics table. Report your teaching activities in the 4 areas of teaching shown below. To provide a more detailed teaching report, use the Teaching Activities Report template or Educator Portfolio template (strongly encouraged). Refer to it here as an attachment (e.g., see attached), and attach it to the CV.

<b><u>Didactic teaching:</u></b> (e.g., lectures, continuing medical education courses, grand rounds, professional development programs, seminars, tutorials)	
Protocol Development (tutorial leader, Mayo Clinic College of Medicine) Health Sciences Grand Rounds	Dates 2008-2012
<b><u>Mentorship:</u></b> (e.g., mentor for medical student, graduate student, resident, clinical or postdoctoral research fellow or junior faculty projects; service as graduate student thesis advisor or committee member)	
8 M.S. candidates in the Clinical Research Master's degree program (Mayo Clinic College of Medicine) Served on five M.S. thesis committees for M.S. candidates in the Clinical Research Master's degree program (Mayo Clinic College of Medicine) Thesis advisor to 4 students in the Biomedical Informatics and Computational Biology M.S. degree program	Dates 2004-2015 2004-2015 2012-2015
<b><u>Clinical teaching:</u></b> (e.g., teaching in the clinic or hospital including bedside teaching, teaching in the operating room, preceptor in clinic)	
	Dates
<b><u>Administrative teaching leadership role:</u></b> (e.g., residency or fellowship director, course or seminar director or co-director)	
Probability and Mathematical Statistics (course director, Macalester College) Introductory Statistics (course director, Macalester College) Mathematical Modeling (course director, Macalester College) Calculus II (course director, Macalester College) Calculus III (course director, Macalester College) Applied Probability (course director, Macalester College) Mathematical Statistics	Dates 1991 1991, 1992 1991, 1992 1992 1992 1992-1998 1993-1999

Stochastic Methods in Management Science (course director, University of Auckland)	1994-1996
Decision Analysis (course director, University of Auckland)	1994-1996
Data Analysis with R (course director, University of Auckland)	1994-1996
Statistics Minor Curriculum Development (Macalester College)	1994-1995
Elementary Statistics (course director, Macalester College)	1995-1996
Linear Algebra (course director, Macalester College)	1996-1998
Senior Capstone (course director, Macalester College)	1996
Applied Multivariate Statistics (course director, Macalester College)	1997-1999
Differential Equations (course director, Macalester College)	1998
Experimental Design and Data analysis (course director, Macalester College)	1998
Introductory Statistical Method I (course director, Mayo Clinic College of Medicine)	1999
Special Topics in Health Sciences Research (course director, Mayo Clinic College of Medicine)	2000-2003
Introductory Statistics Methods II (course director, Mayo Clinic College of Medicine)	2002, 2005
Clinical Trials (course director, Mayo Clinic College of Medicine)	2003-2004
Introduction to Biostatistics (course director, Executive MBA/MS program, Weill Cornell Medicine)	2010, 2011
Biostatistics I (course director, Biostatistics and Data Science MS program, Weill Cornell Medicine)	2017-present
	2018-present

2. Clinical care (duties, dates): To document clinical activities use the table below or, to document extensive clinical activities use the [Clinical Portfolio template](#) (strongly encouraged). Refer to it here as an attachment and attach it to the CV.

N/A

3. Research (duties, dates): Summarize research activities in the table below. Provide key contributions, and annotate key grants and publications or use a [Statement of Key Contributions](#). Refer to it here and attach it to the CV.

Research Activity / Key Contributions	Dates
See Statement of Key Contributions	

4. Administrative Activities (duties, dates): Describe administrative activities in the table below. To document administrative activities more extensively use a supplemental statement, refer to it here and attach it to the CV.

Administrative Activity	Date
Education Committee Member (Health Sciences Research, Mayo Clinic)	2000 to 2002
Education Committee Chair (Health Sciences Research, Mayo Clinic)	2002 to 2007
Education Committee Member (Clinical Research Training Program, Mayo Clinic)	2001 to 2006
Executive Committee Member (Clinical Research Training Program, Mayo Clinic)	2001 to 2005
Master's Examination Committee Member (Clinical Research Training Program, Mayo Clinic)	2002 to 2015
Curriculum Committee Chair (Clinical Research Training Program, Mayo Clinic)	2002 to 2006
Data Safety and Monitoring Board Member (Mayo Clinic Cancer Center)	2003 to 2006
Clinical Studies Oversight Committee Member (Mayo Clinic Cancer Center)	2003 to 2006
Neuro-Oncology Executive Committee Member (Mayo Clinic Cancer Center)	2003 to 2010
Neuro-Oncology Protocol Planning Committee Member (Mayo Clinic Cancer Center)	2003 to 2007
Education Committee Member (Mayo Graduate School)	2004 to 2006
Executive Committee Member (Department of Health Sciences Research, Mayo Clinic)	2004 to 2008
Education Programs Curriculum Committee Member (Center for Translational Activities, Mayo Clinic)	2006 to 2008
Division Chair (Division of Biostatistics, Health Sciences Research, Mayo Clinic)	2006 to 2008
Peer Review Research Committee Member (Department of Surgery, Mayo Clinic)	2011 to 2015

Research Executive Committee Member (Department of Surgery, Mayo Clinic)	2011 to 2015
Research Committee Member (Department of Surgery, Mayo Clinic)	2011 to 2015
Data Safety and Monitoring Board Member (Department of Surgery, Mayo Clinic)	2012 to 2015
Division Chief for Healthcare Policy & Research	2015 to present
Healthcare Policy & Research Promotions Committee Member	2015 to present
Weill Cornell Medicine Data Safety and Monitoring Board (alternative) Co-Chair	2017 to present
Weill Cornell Committee of Review	2018 to present

## H. RESEARCH SUPPORT

Summarize **Past Research** Support:

1. The Mayo Clinic Research Training Program funded by National Center for Research Resources (K30 RR 22296) from 06/1999 to 09/206 ; role: Associate Director
2. Risk Factors for Venous Thromboembolism in the Community funded by NHLBI (R01 HL 66216) from 04/2001 to 04/2005; role: Co-investigator
3. Angiotensin-II Blockade in Mitral Regurgitation funded by NHLBI (R01 HL 64928) from 04/2001 to 03/2005; role: Co-investigator
4. Core 1: Statistical and Administrative Core in: Gene Therapy for Vaso-occlusive disease funded by NHLBI (P01 HL 66958) from 09/2001 to 08/2008; role: Co-investigator
5. Core B: Study Design and Analysis Core in: Molecular Markers of Glioma Initiation & Progression funded by NCI (P01 CA 85799) from 06/2001 to 05/2006; role: Principal Investigator
6. GSK-3 and Associated Pathways in PNET funded by NINDS (R01 NS 40794) from 07/2002 to 11/2005; role: Collaborator
7. Mitochondria and surgical myopreservation in aging funded by NIA (R01 AG 21201) from 09/2002 to 08/2008; role: Consultant
8. Heart Failure in the Community funded by NHLBI ((R01 HL 72435) from 01/2003 to 06/2007; role: Co-investigator
9. Flavopiridol as a Potential Therapy in Multiple Myeloma funded by NCI (R01 CA 98118) funded from 07/2003 to 06/2008; role: Co-investigator
10. MAGE-A3/HPV 16 Peptide Vaccines for Head and Neck Cancer funded by the NIDCR (R01 DE 15324) from 04/2004 to 12/2004; role: Co-investigator
11. Xenograft Model for Studying Amplified EGFR in GBM funded by NCI (R01 NS 49720) from 08/2004 to 05/2006; role: Co-investigator
12. Brain Tumor SPORE – Core B – Biostatistics funded by NCI (P50CA 108961) from 09/2004 to 08/2014; role: Core Director
13. Global Differential Expression Profiling During Sudden Tumor Progression Using the Tumor Dedifferentiation Phenomenon as a Model funded by Mayo Clinic Foundation (CR20) from 04/2006 to 06/2010; role: Co-investigator
14. Measles Virotherapy for Glioblastoma Multiforme funded by NCI (R21 CA 123839) from 08/2006 to 07/2010; role: Co-investigator
15. Utility of Serum and Tissue Biomarkers for Predicting Response to Androgen Deprivation Therapy in the Population of Men with Rising PSA Following Definitive Treatment in: SPORE in Prostate Cancer funded by NCI (P50 CA 91956) from 09/2006 to 08/2013 ; role: Co-investigator
16. SPORE in Prostate Cancer—Biostatistics Core funded by NCI (P50 CA 91956) from 09/2006 to 08/2013; role: Core Director
17. Statistical Responsibilities for American College Of Surgical Oncology Group (ACOSOG) funded by NCI (U10 CA 76001) with subcontract to Mayo from 03/2006 to 11/2014; role: Principal Investigator
18. Epigenetic regulation of temozolomide responsiveness in glioblastoma funded by NCI (R01 CA 127716) from 01/2008 to 12/2012; role: Co-Investigator
19. Correlative Science and Imaging Analysis for Z1031 funded by Breast Cancer Research Foundation (WU-09-200) with subcontract to Mayo from 10/2008 to 09/2009; role: Principal Investigator
20. A phase III randomized Double Blind study of Adjuvant ST1571 (Gleevee) versus Placebo in patients following the Resection of primary gastrointestinal Stromal Tumor (GIST) funded by Novartis from 12/2008 to 06/2009; role: Principal Investigator
21. Mayo Comprehensive Cancer Center Grant funded by NCI (P30CA 15083) from 03/2009 to 07/2015; role: Statistician

22. Novel Biomarkers for Aromatase Inhibitor Therapy funded by NCI (R01 CA 95614) from 04/2009 to 12/2011; role: Principal Investigator
23. Optimizing Measles Virotherapy in the Treatment of Gliomas funded by NCI (R01CA 140620) from 07/2009 to 03/2011; role: Co-investigator
24. ACOSOG Community Clinical Oncology Program (CCOP) Research Base funded by NCI (U10CA 149950) from 06/2010 to 07/2014; role: Co-investigator
25. Treatment patterns of patients with newly diagnosed malignant primary brain tumors funded by Monteris Medical from 09/2010 to 08/2011; role: Principal Investigator
26. Statistical Responsibilities for American College Of Surgical Oncology Group (ACOSOG) in: Industry Supplement of Statistical Responsibilities for American College Of Surgical Oncology Group (ACOSOG) funded by Duke Clinical Research Institute from 12/2010 to 11/2011; role: Principal Investigator
27. N1037 P95HER2 expression in metastatic breast cancer patients treated with trastuzumab on N0337 and NCCTG 98-32-52 funded by BioTheragnostics/BioMerieux from 10/2011 to 3/2012; role: Co-investigator
28. Part 1 N9831F-NCCTG-ICSC Validation study of Quantitative Single Gene Assessment of HER2 mRNA by qRT-PCR and Development and Testing of New HER2 Multi-Gene Signature funded by Genomic Health, Inc. from 04/2012 to 05/2015; role: co-Principal Investigator
29. Therapeutic Strategy to Slow Progression of Calcific Aortic Valve Stenosis funded by National Center for Advancing Translational Sciences (UH2TR 000954) fro 06/2013 to 07/2015; role: Co-investigator
30. Patient Centered: Risk Stratified Surveillance After Curative Research of Colorectal Cancer funded by a subcontract from a PCORI grant (CE-1304-6855) from 03/2014 to 07/2015; role: Principal Investigator
31. Post-Treatment Surveillance in Breast Cancer: Bringing CER to the Alliance funded by a subcontract from a PCORI grant (CE-1304-6543) from 03/2014 to 07/2015; role: Principal Investigator
32. Statistics and Data Center for the Alliance for Clinical Trials in Oncology funded by NCI (U10CA 180882) from 04/2014 to 07/2015; role: Co-investigator
33. Alliance NCORP Research Base funded by NCI (UG1CA 189823) from 08/2014 to 07/2015; role: Co-investigator
34. Improving How We Predict Toxicity for Older Women with Breast Cancer funded by Susan G. Komen Breast Cancer Foundation from 10/2014 to 09/2017; role: Principal Investigator (subsite)
35. Sarcoma Foundation from 11/2015 to 05/2017; role: Principal Investigator
36. Clinical and Translational Science Center (2UL1 TR000457) funded by NIH from 06/01/12 to 05/31/17; role: Co-Investigator
37. SPECS Grant in Lung Cancer (U01CA 157715) funded by NCI from 07/2012 to 06/2018; role: PI of a subcontract
38. Sarcoma SPORE—Biostatistics Core funded by NCI (5U54CA 168512) from 09/2016 to 08/2018; role: Core Director
39. Prostate Cancer Foundation study funded from 07/2017 to 08/2018; role: co-investigator

For **Current extramural and intramural research funding**, provide the following for each award:

1. Source, amount, and duration of support (dates)
2. Name of Principal Investigator
3. Individual's role in project, including percentage (%) effort

**Current Research Support** (duplicate table as needed):

Source	NCI (CA180882) subcontract Alliance
Amount	\$172029
Duration	04/2018 to 02/2023
Principal Investigator	Mandrekar
Your Role in Project	Co-investigator (PI of the subcontract to WCMC)
% Effort	40%

Source	SU2C
Amount	\$13,515

Duration	08/2017 – 06/2020
Principal Investigator	Cantley
Your Role in Project	Co- Investigator
% Effort	5%

Source	National Institutes of Health 1UL1TR002384-01
Amount	\$5,319,707
Duration	09/2017 to 06/2022
Principal Investigator	Imperato-Mcginley
Your Role in Project	Co-Investigator
% Effort	6%

Source	Department of Defense (Subcontract with Duke University, W81XWH-17-1-0372)
Amount	\$170,266
Duration	11/2017 to 10/2020
Principal Investigator	Harpole
Your Role in Project	Principal Investigator (Subsite)
% Effort	10%

Source	National Institutes of Health (P50 CA211024-01A1)
Amount	\$134,759
Duration	07/2017 to 06/2022
Principal Investigator	Rubin
Your Role in Project	Computational Biology and Biostatistics Core Director
% Effort	3%

Source	Bill and Melinda Gates Foundation
Amount	\$89,116
Duration	11/2016 to 05/2020
Principal Investigator	Lee
Your Role in Project	Investigator
% Effort	2%

Source	NIMH, ALACRITY for late- and Mid-Life Mood Disorders (P50 MH113838)
Amount	\$1,014,850
Duration	09/2016 to 08/2021
Principal Investigator	Alexopoulos
Your Role in Project	Investigator
% Effort	5%

Source	NIH, Biomarkers of taxane chemotherapy response/resistance in prostate cancer (R21 CA216800-01A1)
Amount	\$130,500
Duration	04/2018 to 03/2020
Principal Investigator	Giannakakou

Your Role in Project	Investigator
% Effort	2%

Source	Department of Defense, Molecular and clinical correlates with prostate-specific membrane antigen (PSMA)-targeted radionuclide therapy (W81XWH-17-PCRP-IA)
Amount	\$72,380
Duration	07/2018 to 06/2021
Principal Investigator	Tagawa/Beltran/Bander
Your Role in Project	Investigator
% Effort	2%

Source	NIH/NCI, Mechanism-based Targeting of Mantle Cell Lymphoma (P01 CA2144274-01A1)
Amount	\$1,166,145
Duration	09/2018 to 08/2023
Principal Investigator	Chen-Kiang
Your Role in Project	Core Leader
% Effort	8%

Source	NIH, The human distal airway aging project (U01HL145561)
Amount	\$5,688
Duration	01/19
Principal Investigator	Shaykhiev
Your Role in Project	Biostatistician
% Effort	3%

**I. EXTRAMURAL PROFESSIONAL RESPONSIBILITIES**

i.e. – Journal Reviewer, Editorial Boards, Study Sections, Invited Presentations

Activity / Responsibility	Dates
Reviewer The American Math Monthly	1991 to 1999
Gender and Ethnic Division Committee Member North Central Cancer Treatment Group	2002 to 2005
Neuro-Oncology Committee Member North Central Cancer Treatment Group	2002-2006
Reviewer The American Statistician	1994 to 1999
Editorial board member Journal of Statistics Education	1998 to 2003
Reviewer Mayo Clinic Proceedings	2001 to 2004
Reviewer Circulation	2003 to 2006
NCI Review Panel Member Consortium Therapeutic Studies of Primary Central Nervous System Malignancies in Adults	2003, 2008
Reviewer Bioinformatics	2004 to present

NCI Study Section ad hoc Member Scientific Review Group Subcommittee H-Clinical	2004, 2007, 2008
Reviewer Cancer Research	2004 to present
Editorial Board Neuro-Oncology	2004-2014
Reviewer American Journal of Gastroenterology	2005 to 2006
Review Panel Member Academic Public-Private Partnership Program (AP4)	2005
NCI-Avon Foundation Review Panel Member PFP Awards Program	2005 to 2006
NCI Review Panel Member Advanced Proteomic Platforms and Computation Sciences for the NCI Clinical Proteomic Technologies Initiative Review Panel	2006
Executive Committee Member American College of Surgeons Oncology Group	2006 to 2012
NCI Committee Member Breast Cancer Intergroup Committee	2007 to 2009
NCI Committee Member Breast Cancer Intergroup Correlative Sciences Committee	2008 to 2009
NCI Study Section Member Scientific Review Group Subcommittee H-Clinical	2009 to 2012
NCI Steering Committee Member Gastrointestinal Stromal Tumor Working Group	2009-2013
NCI Steering Committee Member Brain Malignancies	2009 to present
NCI Review Panel Member Novel Methodologies	2006
Data Monitoring Committee Member American College of Surgeons Oncology Group	2006 to 2011
Breast Cancer Committee Lead Statistician American College of Surgeons Oncology Group	2006 to 2011
Reviewer Biometrics	2006
NIAID Review Panel Member Cooperative Study Group for Autoimmune Disease Prevention	2006
Clinical Scientific Review Committee Member American College of Surgeons Oncology Group	2006 to 2011
Reviewer International Journal of Cancer	2006 to present
NICHHD Review Panel Member Obstetrical Pharmacology Research Network-Data Coordination and Analyses Center (OPRU-DCAC)	2007
Canada Cancer Society Review Panel Grant Application Review	2007
Editorial Board Journal of Clinical Oncology	2007 to 2010
NIAID Review Panel Member Proteomics Centers for Infectious Diseases and Biodefense	2008
NIDDK Review Panel Member Hepatitis B Clinical Research Network (U01)	2008
NIH Review Panel Member Data Management and Coordinating Center DMCC for the Rare Diseases Clinical Research Network (RDCRN)	2008
NIDDK Review Panel Member Multi-disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network (U01)	2008
Data Monitoring Committee Member	2008-2012

Astra-Zeneca Phase III Trial	
Reviewer EURASIP Journal on Bioinformatics and Systems Biology	2008 to present
NCI Committee Member Clinical Trials Advisory Committee, Operational Efficiencies Working Group	2008 to 2009
NICHHD Review Panel Member Best Pharmaceuticals for Children Act Data Coordinating Center	2009
MN Partnership for Biotechnology and Medical Genomics Review Panel Member Scientific review of grant proposals	2009
NIDA Review Panel Member Data and Statistics Center for NIDA Clinical Trials Network	2009
Thoracic Cancer Committee Lead Statistician American College of Surgeons Oncology Group	2009 to 2011
Reviewer British Journal of Cancer	2009 to present
Reviewer Clinical Trials	2009 to present
Reviewer Plos1	2009 to present
NCI Review Panel Member Clinical Proteomic Technologies for Cancer Initiative: Proteome Characterization Centers	2010
NICHHD Review Panel Member Pediatric Trials Network	2010
Review Panel Member National Cancer Institute of Canada	2010
DOD CDMRP Review Panel Member	2010-2019
Data Monitoring Committee Chair University of Minnesota Iron Study	2010 to 2014
Data Monitoring Committee Member Eli Lilly 14T-MC-JVBB Trial	2010 to 2014
Data Monitoring Committee Incyte RESPONSE Trial	2010 to 2014
Associate Editor Journal of Clinical Oncology	2010 to 2017
Deputy Editor Journal of Clinical Oncology	2017-present
Reviewer Nature	2010, 2013, 2017, 2018
NICHHD Review Panel Member Systematic Review of Neonatal Medicine	2011
NICHHD Review Panel Member Maintenance of Child Health and Development Studies Name and Address Files	2011
Dutch Cancer Society Review Panel Member Scientific Grant Review	2011, 2014, 2015
Reviewer Annals of Surgery	2011 to present
Operations Committee Member Alliance Adult Cancer Cooperative Group	2011 to 2015
Scientific Concept Peer Review Committee Member Alliance Adult Cancer Cooperative Group	2011 to 2014
Data Safety Monitoring Board Chair Kanas University PAD in AA Trial	2011 to 2018
NICHHD Review Panel Member Folic Acid Supplementation and Semen Quality Trial (FAAST)	2012
NIAID Review Panel Member Pre-Clinical Pharmacology and Toxicology Studies	2012
NCI Review Panel Pre-clinical Efficacy and Intermediate Endpoint	2012

NIDA Review Panel Data, Statistics, and Clinical Trial Support for NIDA	2012, 2014
Cancer in the Elderly Committee Lead Statistician Alliance Adult Cancer Cooperative Group	2012 to 2015
NICHHD Review Panel Member Multiple Study Data Coordinating Center for DESPR	2013
Mayo Clinic Review Panel Member Microbiome Program Clinic Trial Funding	2013
NICHHD Review Panel Member Further Investigation into the Causes of Stillbirth Concept Clearance	2013
Publications Committee Member Alliance Adult Cancer Cooperative Group	2013 to 2016
Neuro-Oncology Committee Lead Statistician Alliance Adult Cancer Cooperative Group	2013 to present
FDA Medical Devices Advisory Committee Member General and Plastic Surgery Devices	2013 to present
Damon Runyon Foundation Review Panel Member Clinical Investigator Award	2013 to present
NCI Brain Malignancies Steering Committee member	2013 to present
NCI Review Panel Member PLCO Secondary Studies Proposals	2014, 2015
NIAID Review Panel Member Inner City Asthma Consortium (ICAC3)	2014
Associate Editor Neuro-Oncology	2014 to 2018
Data Safety and Monitoring Board Committee Member NIDDK	2014 to present
NICHHD Review Panel Member P01 Pre-Natal Microbiome Grant Review	2015
NIAID Review Panel Member Centers for Medical Countermeasures against Radiation Consortium (U19)	2015
Cancer Research UK Review Panel Member Biomarker Project Award	2015
Statistical Associate Editor American Journal of Respiratory and Critical Care Medicine	2015 to present
Independent Data Monitoring Committee Member Ariad Phase II trial of AP26113 in non-small cell lung cancer	2015-2018
NIAMS Technical Evaluation Panel Member Clinical Studies Management and Support	2016
NIAID Scientific Review Panel Member Asthma and Allergic Diseases Cooperative Research Centers	2016
NICHD Technical Evaluation Panel Member Best Pharmaceutical for Children Act Data Coordinating Center	2016
NINDS Scientific Review Panel Member Parkinson's Disease Biomarkers Program	2016
Cancer Research United Kingdom Review Panel Member Program Project Submission	2016
Data Safety and Monitoring Board Member The Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) Trial	2016 to present
United States Army Medical Research and Materiel Command (MRMC) Peer Review Panel Member	2016-2018
KNOD Study Section Committee Member	2018 to present
Cancer Moonshot Initiative: Human Tumor Atlas Research Centers (U2C) review panel member	2018
Clinical Research Training Institute Summer Workshop Faculty Member American Society of Hematology	2016 to present
Cancer LinQ Publications Committee Member	2016 to present
STATS.org Statistical Advisory Board Member	2016 to present

NIH/NIAID Asthma and Allergic Diseases Cooperative Research Centers	2017
NCI Program Project Grant (P01) Review Committee Member	2017
Data Safety and Monitoring Board Member Clofazimine in the treatment of pulmonary Mycobacterium avium complex (MAC) disease trial	2017 to present
NCI Oncology E Review Panel Member	2017
ASCO CancerLinQ Research and Publications Committee Member	2017 to present
Conquer Cancer Foundation Grant Selection Committee Member	2017 to present
Independent Data Monitoring Committee Member Takeda Phase III trial of brigatinib in non-small cell lung cancer	2018 to present
NCI Moonshot Initiative, the NCI Human Tumor Atlas Network (HTAN) Review Committee Member	2018
NCI Breast Cancer Steering Committee Member	2018 to present
NCI Program Project Grant (P01) Review V Committee Member	2019

#### J. PROFESSIONAL MEMBERSHIPS

Include medical and scientific societies

Member/Officer/Fellow/Role	Organization	Dates
Member	Operations Research Society of America	1990 to 1993
Officer	Operations Research Society of America	1992
Member	Mathematical Association of America	1991 to 1997
Officer	American Statistical Association	2000 to 2003; 2011 to 2013
Member	American Statistical Association	2000 to present
Member	American Society of Clinical Oncology	2005 to present
Member	Society of Neuro-Oncology	2007-present
Member	International Biometric Society, East North American Region	2006 to present
Officer	International Biometric Society, East North American Region	2008 to 2011
Member	Society of Clinical Trials	2008 to present

#### K. HONORS AND AWARDS

Name of award	Date awarded
Pi Mu Epsilon (Math honorary) - Macalester College	1980
Phi Beta Kappa - Macalester College	1982
Magna Cum Laude - Macalester College	1983
Academic All-American, Division III Volleyball - Macalester College	1983
Fredrick Hennie II Teaching Award - Massachusetts Institute of Technology	1987
Health Sciences Research Distinguished Teaching Award - Mayo Clinic	2004
Macalester College Distinguished Alumni in Science	2015

#### L. BIBLIOGRAPHY

##### 1. Articles in professional peer-reviewed journals

1. **Ballman KV.** Greater emphasis on variation in an introductory statistics course. J Statistics Education. 1997; 5(2).
2. Singh M, Nuttall GA, **Ballman KV**, Mullany CJ, Berger PB, Holmes DR Jr, Bell MR. Effect of abciximab on the outcome of emergency coronary artery bypass grafting after failed percutaneous coronary intervention. Mayo Clin Proc. 2001 Aug; 76(8):784-8. PMID:11499816. DOI:10.1016/S0025-6196(11)63221-7.

3. McConnell JP, Branum EL, **Ballman KV**, Lagerstedt SA, Katzmann JA, Jaffe AS. Gender differences in C-reactive protein concentrations - Confirmation with two sensitive methods. *Clinical Chemistry & Laboratory Medicine*. 2002; 40(1):56-9. PMID:11916271.
4. Aviles RJ, Wright RS, Aviles JM, McDonald F, **Ballman K**, Harker-Murray A, Scott C, Lauer MS, Kopecky SL, Jaffe AS. Long-term prognosis of patients with clinical unstable angina pectoris without elevation of creatine kinase but with elevation of cardiac troponin I levels. *Am J Cardiol*. 2002 Oct 15; 90(8):875-8. PMID:12372578.
5. Brilakis ES, McConnell JP, **Ballman KV**, Klee GG, Berger PB. Lack of association between plasma homocysteine and angiographic coronary artery disease in the era of fortification of cereal grain flour with folic acid. *Atherosclerosis*. 2002 Dec; 165(2):375-81. PMID:12417290.
6. Squires RW, Leung TC, Cyr NS, Allison TG, Johnson BD, **Ballman KV**, Wagner JA, Olson LJ, Frantz RP, Edwards BS, Kushwaha SS, Dearani JA, Daly RC, McGregor CG, Rodeheffer RJ. Partial normalization of the heart rate response to exercise after cardiac transplantation: frequency and relationship to exercise capacity. *Mayo Clin Proc*. 2002 Dec; 77(12):1295-300. PMID:12479515. DOI:10.4065/77.12.1295.
7. Leung TC, **Ballman KV**, Allison TG, Wagner JA, Olson LJ, Frantz RP, Edwards BS, Dearani JA, Daly RC, McGregor CG, Rodeheffer RJ. Clinical predictors of exercise capacity 1 year after cardiac transplantation. *J Heart Lung Transplant*. 2003 Jan; 22(1):16-27. PMID:12531409.
8. Weisberg IS, Park E, **Ballman KV**, Berger P, Nunn M, Suh DS, Breksa AP, Garrow TA, Rozen R. Investigations of a common genetic methyltransferase (BHMT) variant in betaine-homocysteine in coronary artery disease. *Atherosclerosis*. 2003 Apr; 167(2):205-14. PMID:12818402.
9. O'Neill BP, Iturria NJ, Link MJ, Pollock BE, **Ballman KV**, O'Fallon JR. A comparison of surgical resection and stereotactic radiosurgery in the treatment of solitary brain metastases. *Int J Radiat Oncol Biol Phys*. 2003 Apr 1; 55(5):1169-76. PMID:12654423.
10. Takemoto Y, Tanabe K, Chandrasekaran KW, **Ballman KV**, Seward JB, Belohlavek M. Single-plane and biplane echocardiography: Use of targeted scan planes improves the estimates of left ventricular volume and shape for analysis of postinfarction remodeling. *J Am Soc Echocardiogr*. 2003 May; 16(5):448-56. PMID:12724654.
11. Barretto S, **Ballman KV**, Rooke TW, Kullo IJ. Early-onset peripheral arterial occlusive disease: clinical features and determinants of disease severity and location. *Vasc Med*. 2003 May; 8(2):95-100. PMID:14518611.
12. Gami AS, Wright RS, **Ballman KV**, Kopecky SL, Hayes SN. Hormone replacement therapy and risk of acute myocardial infarction in postmenopausal women with diabetes mellitus. *Am J Cardiol*. 2003 May 15; 91(10):1275-7. PMID:12745121.
13. Kanagala R, Murali NS, Friedman PA, Ammash NM, Gersh BJ, **Ballman KV**, Shamsuzzaman ASM, Somers VK. Obstructive sleep apnea and the recurrence of atrial fibrillation. *Circulation*. 2003 May 27; 107(20):2589-94. PMID:12743002.
14. Brilakis ES, Berger PB, **Ballman KV**, Rozen R. Methylenetetrahydrofolate reductase (MTHFR) 677C>T and methionine synthase reductase (MTRR) 66A>G polymorphisms: association with serum homocysteine and angiographic coronary artery disease in the era of flour products fortified with folic acid. *Atherosclerosis*. 2003 Jun; 168(2):315-22. PMID:12801615.
15. Michels VV, Olson TM, Miller FA, **Ballman KV**, Rosales AG, Driscoll DJ. Frequency of development of idiopathic dilated cardiomyopathy among relatives of patients with idiopathic dilated cardiomyopathy. *Am J Cardiol*. 2003 Jun 1; 91(11):1389-92. PMID:12767445.
16. Bunch TJ, White RD, Gersh BJ, Meverden RA, Hodge DO, **Ballman KV**, Hammill SC, Shen WK, Packer DL. Long-term outcomes of out-of-hospital cardiac arrest after successful early defibrillation. *N Engl J Med*. 2003 Jun 26; 348(26):2626-33. PMID:12826637. DOI:10.1056/NEJMoa023053.
17. Gurevitz OT, Friedman PA, Glikson M, Trusty JM, **Ballman KV**, Rosales AG, Hayes DL, Hammill SC, Swerdlow CD. Discrepancies between the upper limit of vulnerability and defibrillation threshold: Prevalence and clinical predictors. *J Cardiovasc Electrophysiol*. 2003 Jul; 14(7):728-32. PMID:12930253.

18. Strome SE, Dong H, Tamura H, Voss SG, Flies DB, Tamada K, Salomao D, Cheville J, Hirano F, Lin W, Kasperbauer JL, **Ballman KV**, Chen L. B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. *Cancer Res.* 2003 Oct 1; 63(19):6501-5. PMID:14559843.
19. Spotila LD, Jacques PF, Berger PB, **Ballman KV**, Ellison RC, Rozen R. Age dependence of the influence of methylenetetrahydrofolate reductase genotype on plasma homocysteine level. *Am J Epidemiol.* 2003 Nov 1; 158(9):871-7. PMID:14585765.
20. Aldape KD, **Ballman KV**, Furth A, Buckner JC, Giannin C, Burger PC, Scheithauer BW, Jenkins RB, James CD. Immunohistochemical detection of EGFRvIII in malignant astrocytomas and evaluation of prognostic significance. *Journal of Neuropathology and Experimental Neurology.* 2004; 63(7):700-707.
21. Gurevitz O, Viskin S, Glikson M, **Ballman KV**, Rosales AG, Shen WK, Hammill SC, Friedman PA. Long-term prognosis of inducible ventricular flutter: not an innocent finding. *Am Heart J.* 2004 Apr; 147(4):649-54. PMID:15077080.
22. Glikson M, Lipchenca I, Viskin S, **Ballman KV**, Trusty JM, Gurevitz OT, Luria DM, Eldar M, Hammill SC, Friedman PA. Long-term outcome of patients who received implantable cardioverter defibrillators for stable ventricular tachycardia. *J Cardiovasc Electrophysiol.* 2004 Jun; 15(6):658-64. PMID:15175060.
23. Aldape KD, **Ballman K**, Furth A, Buckner JC, Giannini C, Burger PC, Scheithauer BW, Jenkins RB, James CD. Immunohistochemical detection of EGFRvIII in high malignancy grade astrocytomas and evaluation of prognostic significance. *J Neuropathol Exp Neurol.* 2004 Jul; 63(7):700-7. PMID:15290895.
24. Kernis SJ, Nkomo VT, Messika-Zeitoun D, Gersh BJ, Sundt TM, **Ballman KV**, Scott CG, Schaff HV, Enriquez-Sarano M. Atrial fibrillation after surgical correction of mitral regurgitation in sinus rhythm - Incidence, outcome, and determinants. *Circulation.* 2004 Oct 19; 110(16):2320-5. PMID:15477410.
25. Kremers HM, Nicola PJ, Crowson CS, **Ballman KV**, Gabriel SE. Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. *Arthritis Rheum.* 2004 Nov; 50(11):3450-7. PMID:15529378.
26. **Ballman KV**, Grill DE, Oberg AL, Therneau TM. Faster cyclic loess: normalizing RNA arrays via linear models. *Bioinformatics.* 2004 Nov 1; 20(16):2778-86. PMID:15166021.
27. Brown PD, Petersen IA, Schomberg PJ, Ivnik RJ, Furth AF, **Ballman KV**, Hammack JE, Buckner JC, Shaw EG, Arusell R. Cognitive function after radiotherapy for supratentorial low-grade glioma: a North Central Cancer Treatment Group prospective study. *Int J Radiat Oncol Biol Phys.* 2005; 58(4):1153-60.
28. Brown P, **Ballman K**, Rummans T, Maurer M, Sloan J, Boeve B, Gupta L, Tang-Wai D, Arusell R, Clark M, Buckner J. Prospective study of quality of life in adults with newly diagnosed high-grade glioma: A North Central Cancer Treatment Group trial. *J Neuro-Oncol.* 2005; 57(3):495-504.
29. Kitange G, Misra A, Law M, Passe S, Kollmeyer TM, Maurer M, **Ballman K**, Feuerstein BG, Jenkins RB. Chromosomal imbalances detected by array comparative genomic hybridization in human oligodendrogliomas and mixed oligoastrocytomas. *Genes Chromosomes Cancer.* 2005 Jan; 42(1):68-77.
30. Abraham RS, **Ballman KV**, Dispenzieri A, Grill DE, Manske MK, Price-Troska TL, Paz NG, Gertz MA, Fonseca R. Functional gene expression analysis of clonal plasma cells identifies a unique molecular profile for light chain amyloidosis. *Blood.* 2005 Jan 15; 105(2):794-803. PMID:15388584.
31. Gurevitz OT, Ammash NM, Malouf JF, Chandrasekaran K, Rosales AG, **Ballman KV**, Hammill SC, White RD, Gersh BJ, Friedman PA. Comparative efficacy of monophasic and biphasic waveforms for transthoracic cardioversion of atrial fibrillation and atrial flutter. *Am Heart J.* 2005 Feb; 149(2):316-21. PMID:15846271. DOI:10.1016/j.ahj.2004.07.007.
32. Maradit-Kremers H, Crowson CS, Nicola PJ, **Ballman KV**, Roger VL, Jacobsen SJ, Gabriel SE. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis-a population-based cohort study. *Arthritis Rheum.* 2005 Feb; 52(2):402-11. PMID:15693010.
33. Nicola PJ, Maradit-Kremers H, Roger VL, Jacobsen SJ, Crowson CS, **Ballman KV**, Gabriel SE. The risk of congestive heart failure in rheumatoid arthritis-a population-based study over 46 years. *Arthritis Rheum.* 2005 Feb; 52(2):412-20. PMID:15692992.

34. Maradit-Kremers H, Nicola PJ, Crowson CS, **Ballman KV**, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum.* 2005 Mar; 52(3):722-32. PMID:15751097.
35. Yang P, Kollmeyer TM, Buckner K, Bamlet W, **Ballman KV**, Jenkins RB. Polymorphisms in GLTSCR1 and ERCC2 are associated with the development of oligodendrogliomas. *Cancer.* 2005 Jun 1; 103(11):2363-72. PMID:15834925. DOI:10.1002/cncr.21028.
36. Galanis E, Buckner JC, Maurer MJ, Kreisberg JI, **Ballman K**, Boni J, Peralba JM, Jenkins RB, Dakhil SR, Morton RF, Jaeckle KA, Scheithauer BW, Dancey J, Hidalgo M, Walsh DJ, North Central Cancer Treatment Group. Phase II trial of temsirolimus (CCI-779) in recurrent glioblastoma multiforme: a North Central Cancer Treatment Group Study. *J Clin Oncol.* 2005 Aug 10; 23(23):5294-304. Epub 2005 Jul 05. PMID:15998902. DOI:10.1200/JCO.2005.23.622.
37. Brown PD, Maurer MJ, Rummans TA, Pollock BE, **Ballman KV**, Sloan JA, Boeve BF, Arusell RM, Clark MM, Buckner JC. A prospective study of quality of life in adults with newly diagnosed high-grade gliomas: the impact of the extent of resection on quality of life and survival. *Neurosurgery.* 2005 Sep; 57(3):495-504; discussion 495-504. PMID:16145528.
38. Crowson CS, Nicola PJ, Maradit Kremers H, O'Fallon WM, Themeau TM, Jacobsen SJ, Roger VL, **Ballman KV**, Gabriel SE. How much of the increased incidence of heart failure in rheumatoid arthritis is attributable to traditional cardiovascular risk factors and ischemic heart disease? *Arthritis Rheum.* 2005 Oct; 52(10):3039-44. PMID:16200583.
39. Laack NN, Brown PD, Ivnik RJ, Furth AF, **Ballman KV**, Hammack JE, Arusell RM, Shaw EG, Buckner JC. Cognitive function after radiotherapy for supratentorial low-grade glioma: A North Central Cancer Treatment Group prospective study. *Int J Radiat Oncol Biol Phys.* 2005 Nov 15; 63(4):1175-83.
40. Miller WL, **Ballman KV**, Hodge DO, Rodeheffer RJ, Hammill SC. Risk factor implications of incidentally discovered uncomplicated bundle branch block. *Mayo Clin Proc.* 2005 Dec; 80(12):1585-90. PMID:16342651. DOI:10.4065/80.12.1585.
41. Brown PD, Foote RL, McLaughlin MP, Halyard MY, **Ballman KV**, Collie AC, Miller RC, Flemming KD, Hallett JW. A historical prospective cohort study of carotid artery stenosis after radiotherapy for head and neck malignancies. *Int J Radiat Oncol Biol Phys.* 2005 Dec 1; 63(5):1361-7. Epub 2005 Sep 19. PMID:16169673. DOI:10.1016/j.ijrobp.2005.05.046.
42. Cooper LT, Henderson SS, **Ballman KV**, Offord KP, Tse TS, Holmes DR, Hurt RD. A prospective, case-control study of tobacco dependence in thromboangiitis obliterans (Buerger's Disease). *Angiology.* 2006 Jan-Feb; 57(1):73-8. PMID:16444459.
43. Nicola PJ, Crowson CS, Maradit-Kremers H, **Ballman KV**, Roger VL, Jacobsen SJ, Gabriel SE. Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. *Arthritis Rheum.* 2006 Jan; 54(1):60-7. PMID:16385496. DOI:10.1002/art.21560.
44. Brown PD, **Ballman KV**, Rummans TA, Maurer MJ, Sloan JA, Boeve BF, Gupta L, Tang-Wai DF, Arusell RM, Clark MM, Buckner JC. Prospective study of quality of life in adults with newly diagnosed high-grade gliomas. *J Neurooncol.* 2006 Feb; 76(3):283-91. PMID:16163448. DOI:10.1007/s11060-005-7020-9.
45. Vanaja DK, **Ballman KV**, Morlan BW, Cheville JC, Neumann RM, Lieber MM, Tindall DJ, Young CY. PDLIM4 repression by hypermethylation as a potential biomarker for prostate cancer. *Clin Cancer Res.* 2006 Feb 15; 12(4):1128-36. PMID:16489065. DOI:10.1158/1078-0432.CCR-05-2072.
46. Jaeckle KA, **Ballman KV**, Rao RD, Jenkins RB, Buckner JC. Current strategies in treatment of oligodendroglioma: evolution of molecular signatures of response. *J Clin Oncol.* 2006 Mar 10; 24(8):1246-52. PMID:16525179. DOI:10.1200/JCO.2005.04.9874.
47. Witt BJ, **Ballman KV**, Brown RD, Meverden RA, Jacobsen SJ, Roger VL. The incidence of stroke after myocardial infarction: a meta-analysis. *Am J Med.* 2006 Apr; 119(4):354.e1-9. PMID:16564779. DOI:10.1016/j.amjmed.2005.10.058.
48. Galanis E, Buckner JC, Maurer MJ, Sykora R, Castillo R, **Ballman KV**, Erickson BJ. Validation of neuroradiologic response assessment in gliomas: measurement by RECIST, two-dimensional, computer-assisted tumor area, and computer-assisted tumor volume methods. *Neuro Oncol.* 2006 Apr; 8(2):156-65. Epub 2006 Mar 02. PMID:16533757. PMCID:1871930. DOI:10.1215/15228517-2005-005.

49. Sarkaria JN, Carlson BL, Schroeder MA, Grogan P, Brown PD, Giannini C, **Ballman KV**, Kitange GJ, Guha A, Pandita A, James CD. Use of an orthotopic xenograft model for assessing the effect of epidermal growth factor receptor amplification on glioblastoma radiation response. *Clin Cancer Res*. 2006 Apr 1; 12(7 Pt 1):2264-71. PMID:16609043. DOI:10.1158/1078-0432.CCR-05-2510.
50. Marshall NE, **Ballman KV**, Michalak JC, Schomberg PJ, Burton GV, Sandler HM, Cascino TL, Jaeckle KA, Buckner JC. Ototoxicity of cisplatin plus standard radiation therapy vs. accelerated radiation therapy in glioblastoma patients. *J Neurooncol*. 2006 May; 77(3):315-20. PMID:16273313. DOI:10.1007/s11060-005-9049-1.
51. Witt BJ, Brown RD, Jacobsen SJ, Weston SA, **Ballman KV**, Meverden RA, Roger VL. Ischemic stroke after heart failure: a community-based study. *Am Heart J*. 2006 Jul; 152(1):102-9. PMID:16824838. DOI:10.1016/j.ahj.2005.10.018.
52. Murillo H, Schmidt LJ, Karter M, Hafner KA, Kondo Y, **Ballman KV**, Vasmataz G, Jenkins RB, Tindall DJ. Prostate cancer cells use genetic and epigenetic mechanisms for progression to androgen independence. *Genes Chromosomes Cancer*. 2006 Jul; 45(7):702-16. PMID:16615098. DOI:10.1002/gcc.20333.
53. Krishnan S, Brown PD, **Ballman KV**, Fiveash JB, Uhm JH, Giannini C, Jaeckle KA, Geoffroy FJ, Nabors LB, Buckner JC, North Central Cancer Treatment Group. Phase I trial of erlotinib with radiation therapy in patients with glioblastoma multiforme: results of North Central Cancer Treatment Group protocol N0177. *Int J Radiat Oncol Biol Phys*. 2006 Jul 15; 65(4):1192-9. Epub 2006 Apr 19. PMID:16626884. DOI:10.1016/j.ijrobp.2006.01.018.
54. Laack NN, **Ballman KV**, Brown PB, O'Neill BP, North Central Cancer Treatment Group. Whole-brain radiotherapy and high-dose methylprednisolone for elderly patients with primary central nervous system lymphoma: Results of North Central Cancer Treatment Group (NCCTG) 96-73-51. *Int J Radiat Oncol Biol Phys*. 2006 Aug 1; 65(5):1429-39. PMID:16863926. DOI:10.1016/j.ijrobp.2006.03.061.
55. Buckner JC, **Ballman KV**, Michalak JC, Burton GV, Cascino TL, Schomberg PJ, Hawkins RB, Scheithauer BW, Sandler HM, Marks RS, O'Fallon JR, North Central Cancer Treatment Group 93-72-52, Southwest Oncology Group 9503 Trials. Phase III trial of carmustine and cisplatin compared with carmustine alone and standard radiation therapy or accelerated radiation therapy in patients with glioblastoma multiforme: North Central Cancer Treatment Group 93-72-52 and Southwest Oncology Group 9503 Trials. *J Clin Oncol*. 2006 Aug 20; 24(24):3871-9. PMID:16921039. DOI:10.1200/JCO.2005.04.6979.
56. Oberg AL, Mahoney DW, **Ballman KV**, Therneau TM. Joint estimation of calibration and expression for high-density oligonucleotide arrays. *Bioinformatics*. 2006 Oct 1; 22(19):2381-7. Epub 2006 Jul 28. PMID:16877757. DOI:10.1093/bioinformatics/btl399.
57. Jenkins RB, Blair H, **Ballman KV**, Giannini C, Arusell RM, Law M, Flynn H, Passe S, Felten S, Brown PD, Shaw EG, Buckner JC. A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. *Cancer Res*. 2006 Oct 15; 66(20):9852-61. PMID:17047046. DOI:10.1158/0008-5472.CAN-06-1796.
58. Babovic-Vuksanovic D, **Ballman K**, Michels V, McGrann P, Lindor N, King B, Camp J, Micic V, Babovic N, Carrero X, Spinner R, O'Neill B. Phase II trial of pirfenidone in adults with neurofibromatosis type 1. *Neurology*. 2006 Nov 28; 67(10):1860-2. Epub 2006 Oct 11. PMID:17035676. DOI:10.1212/01.wnl.0000243231.12248.67.
59. Brown PD, Jensen AW, Felten SJ, **Ballman KV**, Schaefer PL, Jaeckle KA, Cerhan JH, Buckner JC. Detrimental effects of tumor progression on cognitive function of patients with high-grade glioma. *J Clin Oncol*. 2006 Dec 1; 24(34):5427-33. PMID:17135644. DOI:10.1200/JCO.2006.08.5605.
60. Maradit-Kremers H, Nicola PJ, Crowson CS, **Ballman KV**, Jacobsen SJ, Roger VL, Gabriel SE. Raised erythrocyte sedimentation rate signals heart failure in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2007 Jan; 66(1):76-80. Epub 2006 Jul 03. PMID:16818462. PMID:1798392. DOI:10.1136/ard.2006.053710.
61. Mercader M, Sengupta S, Bodner BK, Manecke RG, Cosar EF, Moser MT, **Ballman KV**, Wojcik EM, Kwon ED. Early effects of pharmacological androgen deprivation in human prostate cancer. *BJU Int*. 2007 Jan; 99(1):60-7. PMID:17227493. DOI:10.1111/j.1464-410X.2007.06538.x.

62. **Ballman KV**, Buckner JC, Brown PD, Giannini C, Flynn PJ, LaPlant BR, Jaeckle KA. The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. *Neuro Oncol.* 2007 Jan; 9(1):29-38. Epub 2006 Nov 15 PMID:17108063. PMCID:1828103. DOI:10.1215/15228517-2006-025.
63. Davis JM 3rd, Maradit Kremers H, Crowson CS, Nicola PJ, **Ballman KV**, Thorneau TM, Roger VL, Gabriel SE. Glucocorticoids and cardiovascular events in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum.* 2007 Mar; 56(3):820-30. PMID:17330254.
64. Meyers BF, Downey RJ, Decker PA, Keenan RJ, Siegel BA, Cerfolio RJ, Landreneau RJ, Reed CE, Balfe DM, Dehdashti F, **Ballman KV**, Rusch VW, Putnam JB Jr, American College of Surgeons Oncology Group Z0060. The utility of positron emission tomography in staging of potentially operable carcinoma of the thoracic esophagus: results of the American College of Surgeons Oncology Group Z0060 trial. *J Thorac Cardiovasc Surg.* 2007 Mar; 133(3):738-45. PMID:17320575.
65. Majumdar R, Miller DV, **Ballman KV**, Unnikrishnan G, McKellar SH, Sarkar G, Sreekumar R, Bolander ME, Sundt TM 3rd. Elevated expressions of osteopontin and tenascin C in ascending aortic aneurysms are associated with trileaflet aortic valves as compared with bicuspid aortic valves. *Cardiovasc Pathol.* 2007 May-Jun; 16(3):144-50. Epub 2007 Feb 21. PMID:17502243. DOI:10.1016/j.carpath.2006.12.001.
66. Pelloski CE, **Ballman KV**, Furth AF, Zhang L, Lin E, Sulman EP, Bhat K, McDonald JM, Yung WK, Colman H, Woo SY, Heimberger AB, Suki D, Prados MD, Chang SM, Barker FG, Buckner JC, James CD, Aldape K. Epidermal growth factor receptor variant III status defines clinically distinct subtypes of glioblastoma. *J Clin Oncol.* 2007 Jun 1; 25(16):2288-94. PMID:17538175. DOI:10.1200/JCO.2006.08.0705.
67. Schmidt LJ, **Ballman KV**, Tindall DJ. Inhibition of fatty acid synthase activity in prostate cancer cells by dutasteride. *Prostate.* 2007 Jul 1; 67(10):1111-20. PMID:17477363. DOI:10.1002/pros.20602.
68. Witt BJ, Gami AS, **Ballman KV**, Brown RD Jr, Meverden RA, Jacobsen SJ, Roger VL. The incidence of ischemic stroke in chronic heart failure: a meta-analysis. *J Card Fail.* 2007 Aug; 13(6):489-96. PMID:17675064. DOI:10.1016/j.cardfail.2007.01.009.
69. Buckner JC, O'Fallon JR, Dinapoli RP, Schomberg PJ, Farr G, Schaefer P, Giannini C, Scheithauer BW, **Ballman KV**. Prognosis in patients with anaplastic oligoastrocytoma is associated with histologic grade. *J Neurooncol.* 2007 Sep; 84(3):279-86. Epub 2007 Apr 13. PMID:17431544. DOI:10.1007/s11060-007-9370-y.
70. Locke DE, Decker PA, Sloan JA, Brown PD, Malec JF, Clark MM, Rummans TA, **Ballman KV**, Schaefer PL, Buckner JC. Validation of single-item linear analog scale assessment of quality of life in neuro-oncology patients. *J Pain Symptom Manage.* 2007 Dec; 34(6):628-38. Epub 2007 Aug 20. PMID:17703910. PMCID:2732111. DOI:10.1016/j.jpainsymman.2007.01.016.
71. Thorneau TM, **Ballman KV**. What does PLIER really do? *Cancer Inform.* 2008; 6:423-31. Epub 2008 Aug 27. PMID:19259420. PMCID:2623311.
72. Nakagawa T, Kollmeyer TM, Morlan BW, Anderson SK, Bergstralh EJ, Davis BJ, Asmann YW, Klee GG, **Ballman KV**, Jenkins RB. A tissue biomarker panel predicting systemic progression after PSA recurrence post-definitive prostate cancer therapy. *PLoS One.* 2008; 3(5):e2318. Epub 2008 May 28. PMID:18846227. PMCID:2565588. DOI:10.1371/journal.pone.0002318.
73. Gonzalez A, Maradit Kremers H, Crowson CS, **Ballman KV**, Roger VL, Jacobsen SJ, O'Fallon WM, Gabriel SE. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? *Ann Rheum Dis.* 2008 Jan; 67(1):64-9. Epub 2007 May 21. PMID:17517756. DOI:10.1136/ard.2006.059980.
74. Brown PD, Decker PA, Rummans TA, Clark MM, Frost MH, **Ballman KV**, Arusell RM, Buckner JC. A prospective study of quality of life in adults with newly diagnosed high-grade gliomas: comparison of patient and caregiver ratings of quality of life. *Am J Clin Oncol.* 2008 Apr; 31(2):163-8. PMID:18391601. DOI:10.1097/COC.0b013e318149f1d3.
75. McCollum AK, TenEyck CJ, Stensgard B, Morlan BW, **Ballman KV**, Jenkins RB, Toft DO, Erlichman C. P-Glycoprotein-mediated resistance to Hsp90-directed therapy is eclipsed by the heat shock response. *Cancer Res.* 2008 Sep 15; 68(18):7419-27. PMID:18794130. PMCID:2695926. DOI:10.1158/0008-5472.CAN-07-5175.

76. **Ballman KV.** Genetics and genomics: gene expression microarrays. *Circulation*. 2008 Oct 7; 118(15):1593-7. PMID:18838575. DOI:10.1161/CIRCULATIONAHA.107.714600.
77. Cooper LT Jr, Hare JM, Tazelaar HD, Edwards WD, Starling RC, Deng MC, Menon S, Mullen GM, Jaski B, Bailey KR, Cunningham MW, Dec GW, **Giant Cell Myocarditis Treatment Trial Investigators.** Usefulness of immunosuppression for giant cell myocarditis. *Am J Cardiol*. 2008 Dec 1; 102(11):1535-9. Epub 2008 Sep 18. PMID:19026310. PMCID:2613862. DOI:10.1016/j.amjcard.2008.07.041.
78. Kitange GJ, Carlson BL, Mladek AC, Decker PA, Schroeder MA, Wu W, Grogan PT, Giannini C, **Ballman KV,** Buckner JC, James CD, Sarkaria JN. Evaluation of MGMT promoter methylation status and correlation with temozolomide response in orthotopic glioblastoma xenograft model. *J Neurooncol*. 2009 Mar; 92(1):23-31. Epub 2008 Nov 15. PMID:19011762. PMCID:2790867. DOI:10.1007/s11060-008-9737-8.
79. Dematteo RP, **Ballman KV,** Antonescu CR, Maki RG, Pisters PW, Demetri GD, Blackstein ME, Blanke CD, von Mehren M, Brennan MF, Patel S, McCarter MD, Polikoff JA, Tan BR, Owzar K, American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2009 Mar 28; 373(9669):1097-104. Epub 2009 Mar 18. PMID:19303137. PMCID:2915459. DOI:10.1016/S0140-6736(09)60500-6.
80. Heemers HV, Regan KM, Schmidt LJ, Anderson SK, **Ballman KV,** Tindall DJ. Androgen modulation of coregulator expression in prostate cancer cells. *Mol Endocrinol*. 2009 Apr; 23(4):572-83. Epub 2009 Jan 22. PMID:19164447. PMCID:2667711. DOI:10.1210/me.2008-0363.
81. Wrensch M, Jenkins RB, Chang JS, Yeh RF, Xiao Y, Decker PA, **Ballman KV,** Berger M, Buckner JC, Chang S, Giannini C, Halder C, Kollmeyer TM, Kosel ML, LaChance DH, McCoy L, O'Neill BP, Patoka J, Pico AR, Prados M, Quesenberry C, Rice T, Ryneerson AL, Smirnov I, Tihan T, Wiemels J, Yang P, Wiencke JK. Variants in the CDKN2B and RTEL1 regions are associated with high-grade glioma susceptibility. *Nat Genet*. 2009 Aug; 41(8):905-8. Epub 2009 Jul 05. PMID:19578366. PMCID:2923561. DOI:10.1038/ng.408.
82. Carlson BL, Grogan PT, Mladek AC, Schroeder MA, Kitange GJ, Decker PA, Giannini C, Wu W, **Ballman KA,** James CD, Sarkaria JN. Radiosensitizing effects of temozolomide observed in vivo only in a subset of O6-methylguanine-DNA methyltransferase methylated glioblastoma multiforme xenografts. *Int J Radiat Oncol Biol Phys*. 2009 Sep 1; 75(1):212-9. PMID:19695438. PMCID:2773462. DOI:10.1016/j.ijrobp.2009.04.026.
83. Drucker KL, Kitange GJ, Kollmeyer TM, Law ME, Passe S, Ryneerson AL, Blair H, Soderberg CL, Morlan BW, **Ballman KV,** Giannini C, Jenkins RB. Characterization and gene expression profiling in glioma cell lines with deletion of chromosome 19 before and after microcell-mediated restoration of normal human chromosome 19. *Genes Chromosomes Cancer*. 2009 Oct; 48(10):854-64. PMID:19544381. PMCID:3190979. DOI:10.1002/gcc.20688.
84. Jaekle KA, **Ballman K,** Furth A, Buckner JC. Correlation of enzyme-inducing anticonvulsant use with outcome of patients with glioblastoma. *Neurology*. 2009 Oct 13; 73(15):1207-13. PMID:19822870. PMCID:2764724. DOI:10.1212/WNL.0b013e3181bbfec9.
85. Schmidt LJ, Regan KM, Anderson SK, Sun Z, **Ballman KV,** Tindall DJ. Effects of the 5 alpha-reductase inhibitor dutasteride on gene expression in prostate cancer xenografts. *Prostate*. 2009 Dec 1; 69(16):1730-43. PMID:19676081. PMCID:2783419. DOI:10.1002/pros.21022.
86. Hillman SL, Mandrekar SJ, Bot B, DeMatteo RP, Perez EA, **Ballman KV,** Nelson H, Buckner JC, Sargent DJ. Evaluation of the value of attribution in the interpretation of adverse event data: a North Central Cancer Treatment Group and American College of Surgeons Oncology Group investigation. *J Clin Oncol*. 2010 Jun 20; 28(18):3002-7. Epub 2010 May 17. PMID:20479400. PMCID:2903334. DOI:10.1200/JCO.2009.27.4282.
87. Wilke LG, **Ballman KV,** McCall LM, Giuliano AE, Whitworth PW, Blumencranz PW, Reintgen DS, Burak WE, Leitch AM, Hunt KK. Adherence to the National Quality Forum (NQF) breast cancer measures within cancer clinical trials: a review from ACOSOG Z0010. *Ann Surg Oncol*. 2010 Aug; 17(8):1989-94. Epub 2010 Mar 23. PMID:20309640. PMCID:2950006. DOI:10.1245/s10434-010-0980-9.

88. Jaeckle KA, **Ballman KV**, Giannini C, Schomberg PJ, Ames MM, Reid JM, McGovern RM, Safgren SL, Galanis E, Uhm JH, Brown PD, Hammack JE, Arusell R, Nikcevich DA, Morton RF, Wender DB, Buckner JC. Phase II NCCTG trial of RT + irinotecan and adjuvant BCNU plus irinotecan for newly diagnosed GBM. *J Neurooncol.* 2010 Aug; 99(1):73-80. Epub 2010 Jan 09. PMID:20063115. PMCID:2897141. DOI:10.1007/s11060-009-0103-2.
89. Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, Saha S, Hunt KK, Morrow M, **Ballman K**. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg.* 2010 Sep; 252(3):426-32; discussion 432-3. PMID:20739842. DOI:10.1097/SLA.0b013e3181f08f32.
90. Kitange GJ, Carlson BL, Schroeder MA, Decker PA, Morlan BW, Wu W, **Ballman KV**, Giannini C, Sarkaria JN. Expression of CD74 in high grade gliomas: a potential role in temozolomide resistance. *J Neurooncol.* 2010 Nov; 100(2):177-86. Epub 2010 May 05. PMID:20443131. PMCID:3233976. DOI:10.1007/s11060-010-0186-9.
91. Shi Q, You YN, Nelson H, Allen MS, Winchester D, Stewart A, Young-Fadok T, Decker PA, Green EM, Holton SJ, **Ballman KV**. Cancer registries: a novel alternative to long-term clinical trial follow-up based on results of a comparative study. *Clin Trials.* 2010 Dec; 7(6):686-95. Epub 2010 Aug 20. PMID:20729254. DOI:10.1177/1740774510380953.
92. Giuliano AE, Hunt KK, **Ballman KV**, Beitsch PD, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, McCall LM, Morrow M. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA.* 2011 Feb 9; 305(6):569-75. PMID:21304082. DOI:10.1001/jama.2011.90.
93. Darling GE, Allen MS, Decker PA, **Ballman K**, Malthaner RA, Inculet RI, Jones DR, McKenna RJ, Landreneau RJ, Rusch VW, Putnam JB. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. *J Thorac Cardiovasc Surg.* 2011 Mar; 141(3):662-70. PMID:21335122. DOI:10.1016/j.jtcvs.2010.11.008.
94. Heemers HV, Schmidt LJ, Sun Z, Regan KM, Anderson SK, Duncan K, Wang D, Liu S, **Ballman KV**, Tindall DJ. Identification of a clinically relevant androgen-dependent gene signature in prostate cancer. *Cancer Res.* 2011 Mar 1; 71(5):1978-88. Epub 2011 Feb 15. PMID:21324924. PMCID:3077061. DOI:10.1158/0008-5472.CAN-10-2512.
95. Darling GE, Allen MS, Decker PA, **Ballman K**, Malthaner RA, Inculet RI, Jones DR, McKenna RJ, Landreneau RJ, Putnam JB. Number of lymph nodes harvested from a mediastinal lymphadenectomy: results of the randomized, prospective American College of Surgeons Oncology Group Z0030 trial. *Chest.* 2011 May; 139(5):1124-9. Epub 2010 Sep 09. PMID:20829340. PMCID:3087457. DOI:10.1378/chest.10-0859.
96. Uhm JH, **Ballman KV**, Wu W, Giannini C, Krauss JC, Buckner JC, James CD, Scheithauer BW, Behrens RJ, Flynn PJ, Schaefer PL, Dakhil SR, Jaeckle KA. Phase II evaluation of gefitinib in patients with newly diagnosed Grade 4 astrocytoma: Mayo/North Central Cancer Treatment Group Study N0074. *Int J Radiat Oncol Biol Phys.* 2011 Jun 1; 80(2):347-53. Epub 2010 May 25. PMID:20510539. DOI:10.1016/j.ijrobp.2010.01.070.
97. Giuliano AE, Hawes D, **Ballman KV**, Whitworth PW, Blumencranz PW, Reintgen DS, Morrow M, Leitch AM, Hunt KK, McCall LM, Abati A, Cote R. Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. *JAMA.* 2011 Jul 27; 306(4):385-93. PMID:21791687. DOI:10.1001/jama.2011.1034.
98. Jaeckle KA, Decker PA, **Ballman KV**, Flynn PJ, Giannini C, Scheithauer BW, Jenkins RB, Buckner JC. Transformation of low grade glioma and correlation with outcome: an NCCTG database analysis. *J Neurooncol.* 2011 Aug; 104(1):253-9. Epub 2010 Dec 12. PMID:21153680. DOI:10.1007/s11060-010-0476-2.
99. Laack NN, O'Neill BP, **Ballman KV**, O'Fallon JR, Carrero XW, Kurtin PJ, Scheithauer BW, Brown PD, Habermann TM, Colgan JP, Gilbert MR, Hawkins RB, Morton RF, Windschitl HE, Fitch TR, Pajon ER Jr, North Central Cancer Treatment Group and Mayo Clinic. CHOD/BVAM chemotherapy and whole-brain radiotherapy for newly diagnosed primary central nervous system lymphoma. *Int J Radiat Oncol*

- Biol Phys. 2011 Oct 1; 81(2):476-82. Epub 2010 Aug 26 PMID:20800387. PMCID:4335722. DOI:10.1016/j.ijrobp.2010.06.002.
100. Rusch VW, Hawes D, Decker PA, Martin SE, Abati A, Landreneau RJ, Patterson GA, Inculet RI, Jones DR, Malthaner RA, Cohen RG, **Ballman K**, Putnam JB Jr, Cote RJ. Occult metastases in lymph nodes predict survival in resectable non-small-cell lung cancer: report of the ACOSOG Z0040 trial. *J Clin Oncol*. 2011 Nov 10; 29(32):4313-9. Epub 2011 Oct 11. PMID:21990404. PMCID:3221530. DOI:10.1200/JCO.2011.35.2500.
  101. Toussaint LG III, Nilson AE, Goble JM, **Ballman KV**, James CD, Lefranc F, Kiss R, Uhm JH. Galectin-1, a gene preferentially expressed at the tumor margin, promotes glioblastoma cell invasion. *Mol Cancer*. 2012; 11:32. Epub 2012 May 14. PMID:22583806. PMCID:3407025. DOI:10.1186/1476-4598-11-32.
  102. Deley MC, **Ballman KV**, Marandet J, Sargent D. Taking the long view: how to design a series of Phase III trials to maximize cumulative therapeutic benefit. *Clin Trials*. 2012 Jun; 9(3):283-92. Epub 2012 May 08. PMID:22569743. PMCID:3904223. DOI:10.1177/1740774512443430.
  103. Ellis MJ, Ding L, Shen D, Luo J, Suman VJ, Wallis JW, Van Tine BA, Hoog J, Goiffon RJ, Goldstein TC, Ng S, Lin L, Crowder R, Snider J, **Ballman K**, Weber J, Chen K, Koboldt DC, Kandoth C, Schierding WS, McMichael JF, Miller CA, Lu C, Harris CC, McLellan MD, Wendl MC, DeSchryver K, Allred DC, Esserman L, Unzeitig G, Margenthaler J, Babiera GV, Marcom PK, Guenther JM, Leitch M, Hunt K, Olson J, Tao Y, Maher CA, Fulton LL, Fulton RS, Harrison M, Oberkfell B, Du F, Demeter R, Vickery TL, Elhammali A, Piwnica-Worms H, McDonald S, Watson M, Dooling DJ, Ota D, Chang LW, Bose R, Ley TJ, Piwnica-Worms D, Stuart JM, Wilson RK, Mardis ER. Whole-genome analysis informs breast cancer response to aromatase inhibition. *Nature*. 2012 Jun 21; 486(7403):353-60. Epub 2012 Jun 10. PMID:22722193. PMCID:3383766. DOI:10.1038/nature11143.
  104. McCarter MD, Antonescu CR, **Ballman KV**, Maki RG, Pisters PW, Demetri GD, Blanke CD, von Mehren M, Brennan MF, McCall L, Ota DM, DeMatteo RP, American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant Gist Study Team. Microscopically positive margins for primary gastrointestinal stromal tumors: analysis of risk factors and tumor recurrence. *J Am Coll Surg*. 2012 Jul; 215(1):53-9; discussion 59-60. PMID:22726733. PMCID:3383609. DOI:10.1016/j.jamcollsurg.2012.05.008.
  105. Hunt KK, **Ballman KV**, McCall LM, Boughey JC, Mittendorf EA, Cox CE, Whitworth PW, Beitsch PD, Leitch AM, Buchholz TA, Morrow MA, Giuliano AE. Factors associated with local-regional recurrence after a negative sentinel node dissection: results of the ACOSOG Z0010 trial. *Ann Surg*. 2012 Sep; 256(3):428-36. PMID:22868365. DOI:10.1097/SLA.0b013e3182654494.
  106. O'Brien KM, Orlow I, Antonescu CR, **Ballman K**, McCall L, DeMatteo R, Engel LS. Gastrointestinal stromal tumors, somatic mutations and candidate genetic risk variants. *PLoS One*. 2013; 8(4):e62119. Epub 2013 Apr 18. PMID:23637977. PMCID:3630216. DOI:10.1371/journal.pone.0062119.
  107. Erho N, Crisan A, Vergara IA, Mitra AP, Ghadessi M, Buerki C, Bergstralh EJ, Kollmeyer T, Fink S, Haddad Z, Zimmermann B, Sierocinski T, **Ballman KV**, Triche TJ, Black PC, Karnes RJ, Klee G, Davicioni E, Jenkins RB. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. *PLoS One*. 2013; 8(6):e66855. Epub 2013 Jun 24. PMID:23826159. PMCID:3691249. DOI:10.1371/journal.pone.0066855.
  108. Garraway LA, Verweij J, **Ballman KV**. Precision oncology: an overview. *J Clin Oncol*. 2013 May 20; 31(15):1803-5. Epub 2013 Apr 15. PMID:23589545. DOI:10.1200/JCO.2013.49.4799.
  109. Freedman RA, Pitcher B, Keating NL, **Ballman KV**, Mandelblatt J, Kornblith AB, Kimmick GG, Hurria A, Winer EP, Hudis CA, Cohen HJ, Muss HB, Alliance for Clinical Trials in Oncology. Cognitive function in older women with breast cancer treated with standard chemotherapy and capecitabine on Cancer and Leukemia Group B 49907. *Breast Cancer Res Treat*. 2013 Jun; 139(2):607-16. Epub 2013 May 17. PMID:23681403. PMCID:3920483. DOI:10.1007/s10549-013-2562-6.
  110. Cen L, Carlson BL, Pokorny JL, Mladek AC, Grogan PT, Schroeder MA, Decker PA, Anderson SK, Giannini C, Wu W, **Ballman KV**, Kitange GJ, Sarkaria JN. Efficacy of protracted temozolomide dosing is limited in MGMT unmethylated GBM xenograft models. *Neuro Oncol*. 2013 Jun; 15(6):735-46. Epub 2013 Mar 10. PMID:23479134. PMCID:3661094. DOI:10.1093/neuonc/not010.
  111. Crozier JA, Moreno-Aspitia A, **Ballman KV**, Dueck AC, Pockaj BA, Perez EA. Effect of body mass index on tumor characteristics and disease-free survival in patients from the HER2-positive adjuvant

- trastuzumab trial N9831. *Cancer*. 2013 Jul 1; 119(13):2447-54. Epub 2013 Apr 12. PMID:23585192. PMCID:3686994. DOI:10.1002/cncr.28051.
112. Gami AS, Olson EJ, Shen WK, Wright RS, **Ballman KV**, Hodge DO, Herges RM, Howard DE, Somers VK. Obstructive sleep apnea and the risk of sudden cardiac death: a longitudinal study of 10,701 adults. *J Am Coll Cardiol*. 2013 Aug 13; 62(7):610-6. Epub 2013 Jun 13. PMID:23770166. PMCID:3851022. DOI:10.1016/j.jacc.2013.04.080.
113. DeMatteo RP, **Ballman KV**, Antonescu CR, Corless C, Kolesnikova V, von Mehren M, McCarter MD, Norton J, Maki RG, Pisters PW, Demetri GD, Brennan MF, Owzar K, American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team for the Alliance for Clinical Trials in Oncology. Long-term results of adjuvant imatinib mesylate in localized, high-risk, primary gastrointestinal stromal tumor: ACOSOG Z9000 (Alliance) intergroup phase 2 trial. *Ann Surg*. 2013 Sep; 258(3):422-9. PMID:23860199. PMCID:4041735. DOI:10.1097/SLA.0b013e3182a15eb7.
114. Wildiers H, Mauer M, Pallis A, Hurria A, Mohile SG, Luciani A, Curigliano G, Extermann M, Lichtman SM, **Ballman K**, Cohen HJ, Muss H, Wedding U. End points and trial design in geriatric oncology research: a joint European organisation for research and treatment of cancer--Alliance for Clinical Trials in Oncology--International Society Of Geriatric Oncology position article. *J Clin Oncol*. 2013 Oct 10; 31(29):3711-8. Epub 2013 Sep 09. PMID:24019549. DOI:10.1200/JCO.2013.49.6125.
115. Dueck AC, Reinholz MM, Geiger XJ, Tenner K, **Ballman K**, Jenkins RB, Riehle D, Chen B, McCullough AE, Davidson NE, Martino S, Sledge GW, Kaufman PA, Kutteh LA, Gralow J, Harris LN, Ingle JN, Lingle WL, Perez EA. Impact of c-MYC protein expression on outcome of patients with early-stage HER2+ breast cancer treated with adjuvant trastuzumab NCCTG (alliance) N9831. *Clin Cancer Res*. 2013 Oct 15; 19(20):5798-807. Epub 2013 Aug 21. PMID:23965903. PMCID:3805021. DOI:10.1158/1078-0432.CCR-13-0558.
116. Karnes RJ, Bergstralh EJ, Davicioni E, Ghadessi M, Buerki C, Mitra AP, Crisan A, Erho N, Vergara IA, Lam LL, Carlson R, Thompson DJ, Haddad Z, Zimmermann B, Sierocinski T, Triche TJ, Kollmeyer T, **Ballman KV**, Black PC, Klee GG, Jenkins RB. Validation of a genomic classifier that predicts metastasis following radical prostatectomy in an at risk patient population. *J Urol*. 2013 Dec; 190(6):2047-53. Epub 2013 Jun 11. PMID:23770138. PMCID:4097302. DOI:10.1016/j.juro.2013.06.017.
117. Barginear MF, Muss H, Kimmick G, Owusu C, Mrozek E, Shahrokni A, **Ballman K**, Hurria A. Breast cancer and aging: Results of the U13 conference breast cancer panel. *Breast Cancer Res Treat*. 2014; 146(1):1-6.
118. Joensuu H, Eriksson M, Hall KS, Hartmann JT, Pink D, Schutte J, Ramadori G, Hohenberger P, Duyster J, Al-Batran SE, Schlemmer M, Bauer S, Wardelmann E, Sarlomo-Rikala M, Nilsson B, Sihto H, **Ballman KV**, Leinonen M, Dematteo RP, Reichardt P. Risk factors for gastrointestinal stromal tumor recurrence in patients treated with adjuvant imatinib. *Cancer*. 2014; 120(15):2325-33.
119. Batdorf NJ, Mubang R, Whitney G, **Ballman K**, Lovely J, Grubbs P, Lisa B, Hinckley A, Lemaine V, Saint-Cyr M. Abstract 113: Comparison of Outcomes for Patients Undergoing Free Flap Autologous Breast Reconstruction Utilizing a Multimodal Enhanced Recovery Pathway versus Traditional Care. *Plast Reconstr Surg*. 2014 Mar; 133(3 Suppl):130. PMID:25942224. DOI:10.1097/01.prs.0000444938.78110.c2.
120. Grogan EL, Deppen SA, **Ballman KV**, Andrade GM, Verdial FC, Aldrich MC, Chen CL, Decker PA, Harpole DH, Cerfolio RJ, Keenan RJ, Jones DR, D'Amico TA, Shrager JB, Meyers BF, Putnam JB Jr. Accuracy of fluorodeoxyglucose-positron emission tomography within the clinical practice of the American College of Surgeons Oncology Group Z4031 trial to diagnose clinical stage I non-small cell lung cancer. *Ann Thorac Surg*. 2014 Apr; 97(4):1142-8. Epub 2014 Feb 25. PMID:24576597. PMCID:4008142. DOI:10.1016/j.athoracsur.2013.12.043.
121. Corless CL, **Ballman KV**, Antonescu CR, Kolesnikova V, Maki RG, Pisters PW, Blackstein ME, Blanke CD, Demetri GD, Heinrich MC, von Mehren M, Patel S, McCarter MD, Owzar K, DeMatteo RP. Pathologic and molecular features correlate with long-term outcome after adjuvant therapy of resected primary GI stromal tumor: the ACOSOG Z9001 trial. *J Clin Oncol*. 2014 May 20; 32(15):1563-70. Epub 2014 Mar 17. PMID:24638003. PMCID:4026579. DOI:10.1200/JCO.2013.51.2046.
122. Hurria A, Dale W, Mooney M, Rowland JH, **Ballman KV**, Cohen HJ, Muss HB, Schilsky RL, Ferrell B, Extermann M, Schmader KE, Mohile SG. Designing Therapeutic Clinical Trials for Older and Frail

- Adults With Cancer: U13 Conference Recommendations. *J Clin Oncol.* 2014 Aug 20;32(24):2587-94. Epub 2014 Jul 29. PMID:25071116. PMCID:4129504. DOI:10.1200/JCO.2013.55.0418.
123. Klepin HD, Pitcher BN, **Ballman KV**, Kornblith AB, Hurria A, Winer EP, Hudis C, Cohen HJ, Muss HB, Kimmick GG. Comorbidity, chemotherapy toxicity, and outcomes among older women receiving adjuvant chemotherapy for breast cancer on a clinical trial: CALGB 49907 and CALGB 361004 (alliance). *J Oncol Pract.* 2014 Sep; 10(5):e285-92. Epub 2014 Jul 29. PMID:25074878. PMCID:4161730. DOI:10.1200/JOP.2014.001388.
124. Cheng H, **Ballman K**, Vassilakopoulou M, Dueck AC, Reinholz MM, Tenner K, Gralow J, Hudis C, Davidson NE, Fountzilas G, McCullough AE, Chen B, Psyrri A, Rimm DL, Perez EA. EGFR expression is associated with decreased benefit from trastuzumab in the NCCTG N9831 (Alliance) trial. *Br J Cancer.* 2014 Sep 9; 111(6):1065-71. Epub 2014 Aug 12. PMID:25117817. DOI:10.1038/bjc.2014.442.
125. Boughey JC, McCall LM, **Ballman KV**, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, Leitch AM, Flippo-Morton T, Hunt KK. Tumor biology correlates with rates of breast-conserving surgery and pathologic complete response after neoadjuvant chemotherapy for breast cancer: findings from the ACOSOG Z1071 (Alliance) Prospective Multicenter Clinical Trial. *Ann Surg.* 2014 Oct; 260(4):608-14; discussion 614-6. PMID:25203877. PMCID:4159769. DOI:10.1097/SLA.0000000000000924.
126. Degnim AC, Hoskin TL, Brahmbhatt RD, Warren-Peled A, Loprinzi M, Pavey ES, Boughey JC, Hieken TJ, Jacobson S, Lemaine V, Jakub JW, Irwin C, Foster RD, Sbitany H, Saint-Cyr M, Duralde E, Ramaker S, Chin R, Sieg M, Wildeman M, Scow JS, Patel R, **Ballman K**, Baddour LM, Esserman LJ. Randomized trial of drain antisepsis after mastectomy and immediate prosthetic breast reconstruction. *Ann Surg Oncol.* 2014 Oct; 21(10):3240-8. Epub 2014 Aug 06. PMID:25096386. PMCID:4373621. DOI:10.1245/s10434-014-3918-9.
127. Onkendi EO, Jimenez RE, Spears GM, Harmsen WS, **Ballman KV**, Hieken TJ. Surgical treatment of borderline and malignant phyllodes tumors: the effect of the extent of resection and tumor characteristics on patient outcome. *Ann Surg Oncol.* 2014 Oct; 21(10):3304-9. Epub 2014 Jul 18. PMID:25034817. DOI:10.1245/s10434-014-3909-x.
128. Norton N, Olson RM, Pegram M, Tenner K, **Ballman KV**, Clynes R, Knutson KL, Perez EA. Association studies of Fcγ receptor polymorphisms with outcome in HER2+ breast cancer patients treated with trastuzumab in NCCTG (Alliance) Trial N9831. *Cancer Immunol Res.* 2014 Oct; 2(10):962-9. Epub 2014 Jul 02. PMID:24989892. PMCID:4215796. DOI:10.1158/2326-6066.CIR-14-0059.
129. Reardon DA, **Ballman KV**, Buckner JC, Chang SM, Ellingson BM. Impact of imaging measurements on response assessment in glioblastoma clinical trials. *Neuro Oncol.* 2014 Oct; 16 Suppl 7:vii24-35. PMID:25313236. PMCID:4195531. DOI:10.1093/neuonc/nou286.
130. Wen PY, Cloughesy TF, Ellingson BM, Reardon DA, Fine HA, Abrey L, **Ballman K**, Bendszuz M, Buckner J, Chang SM, Prados MD, Pope WB, Gregory Sorensen A, van den Bent M, Yung WK. Report of the Jumpstarting Brain Tumor Drug Development Coalition and FDA clinical trials neuroimaging endpoint workshop (January 30, 2014, Bethesda MD). *Neuro Oncol.* 2014 Oct; 16 Suppl 7:vii36-47. PMID:25313237. PMCID:4195530. DOI:10.1093/neuonc/nou226.
131. Jagsi R, Chadha M, Moni J, **Ballman K**, Laurie F, Buchholz TA, Giuliano A, Haffty BG. Radiation field design in the ACOSOG Z0011 (Alliance) Trial. *J Clin Oncol.* 2014 Nov 10; 32(32):3600-6. Epub 2014 Aug 18. PMID:25135994. PMCID:4220042. DOI:10.1200/JCO.2014.56.5838.
132. Necela BM, Crozier JA, Andorfer CA, Lewis-Tuffin L, Kachergus JM, Geiger XJ, Kalari KR, Serie DJ, Sun Z, Aspita AM, O'Shannessy DJ, Maltzman JD, McCullough AE, Pockaj BA, Cunliffe HE, **Ballman KV**, Thompson EA, Perez EA. Folate Receptor-alpha (FOLR1) Expression and Function in Triple Negative Tumors. *PLoS One.* 2015; 10(3):e0122209. Epub 2015 Mar 27. PMID:25816016. PMCID:4376802. DOI:10.1371/journal.pone.0122209.
133. Grotz TE, Puig CA, Perkins S, **Ballman K**, Hieken TJ. Management of regional lymph nodes in the elderly melanoma patient: patient selection, accuracy and prognostic implications. *Eur J Surg Oncol.* 2015 Jan; 41(1):157-64. Epub 2014 Oct 30. PMID:25468751. DOI:10.1016/j.ejso.2014.10.051.
134. Alexander BM, Galanis E, Yung WK, **Ballman KV**, Boyett JM, Cloughesy TF, Degroot JF, Huse JT, Mann B, Mason W, Mellinghoff IK, Mikkelsen T, Mischel PS, O'Neill BP, Prados MD, Sarkaria JN, Tawab-Amiri A, Trippa L, Ye X, Ligon KL, Berry DA, Wen PY. Brain Malignancy Steering Committee clinical trials planning workshop: report from the Targeted Therapies Working Group. *Neuro Oncol.*

- 2015 Feb; 17(2):180-8. Epub 2014 Aug 26. PMID:25165194. PMCID:4288520. DOI:10.1093/neuonc/nou154.
135. Boughey JC, **Ballman KV**, Hunt KK, McCall LM, Mittendorf EA, Ahrendt GM, Wilke LG, Le-Petross HT. Axillary Ultrasound After Neoadjuvant Chemotherapy and Its Impact on Sentinel Lymph Node Surgery: Results From the American College of Surgeons Oncology Group Z1071 Trial (Alliance). *J Clin Oncol*. 2015 Feb 02. PMID:25646192. DOI:10.1200/JCO.2014.57.8401.
136. Batdorf NJ, Lemaine V, Lovely JK, **Ballman KV**, Goede WJ, Martinez-Jorge J, Booth-Kowalczyk AL, Grubbs PL, Bungum LD, Saint-Cyr M. Enhanced recovery after surgery in microvascular breast reconstruction. *J Plast Reconstr Aesthet Surg*. 2015 Mar; 68(3):395-402. Epub 2014 Nov 21. PMID:25488326. DOI:10.1016/j.bjps.2014.11.014.
137. Perez EA, Thompson EA, **Ballman KV**, Anderson SK, Asmann YW, Kalari KR, Eckel-Passow JE, Dueck AC, Tenner KS, Jen J, Fan JB, Geiger XJ, McCullough AE, Chen B, Jenkins RB, Sledge GW, Winer EP, Gralow JR, Reinholz MM. Genomic analysis reveals that immune function genes are strongly linked to clinical outcome in the North Central Cancer Treatment Group n9831 Adjuvant Trastuzumab Trial. *J Clin Oncol*. 2015 Mar 1; 33(7):701-8. Epub 2015 Jan 20. PMID:25605861. PMCID:4334774. DOI:10.1200/JCO.2014.57.6298.
138. Mohan AT, Rammos CK, Gaba P, Schupbach J, Goede WJ, **Ballman K**, Batdorf N, Cheng A, Saint-Cyr M. Modified aesthetic abdominoplasty approach in perforator free-flap breast reconstruction: Impact of drain free donor site on patient outcomes. *J Plast Reconstr Aesthet Surg*. 2015. 68(6):800-809. PMID:25843908. DOI:10.1016/j.bjps.2015.03.008.
139. Laungani AT, Van Alphen N, Christner JA, Lachman N, Pawlina W, **Ballman KV**, Saint-Cyr M. Three-dimensional CT angiography assessment of the impact of the dermis and the subdermal plexus in DIEP flap perfusion. *J Plast Reconstr Aesthet Surg*. 2015 Apr; 68(4):525-30. Epub 2015 Jan 07. PMID:25665491. DOI:10.1016/j.bjps.2014.12.004.
140. Mittendorf EA, **Ballman KV**, McCall LM, Yi M, Sahin AA, Bedrosian I, Hansen N, Gabram S, Hurd T, Giuliano AE, Hunt KK. Evaluation of the Stage IB Designation of the American Joint Committee on Cancer Staging System in Breast Cancer. *J Clin Oncol*. 2015 Apr 1; 33(10):1119-27. Epub 2014 Dec 08. PMID:25488970. PMCID:4372850. DOI:10.1200/JCO.2014.57.2958.
141. Jatoti A, Muss H, Allred JB, Cohen HJ, **Ballman K**, Hopkins JO, Gajra A, Lafky J, Wolff A, Kottschade L, Gralow J, Hurria A. Psychooncology. 2015 May 20. doi: 10.1002/pon.3850. [Epub ahead of print] PMID: 25994447
142. O'Sullivan CC, Bradbury I, Campbell C, Spielmann M, Perez EA, Joensuu H, Costantino JP, Delaloge S, Rastogi P, Zardavas D, **Ballman KV**, Holmes E, de Azambuja E, Piccart-Gebhart M, Zujewski JA, Gelber RD. Efficacy of Adjuvant Trastuzumab for Patients With Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer and Tumors  $\leq 2$  cm: A Meta-Analysis of the Randomized Trastuzumab Trials. *J Clin Oncol*. 2015 Aug 20;33(24):2600-8. doi: 10.1200/JCO.2015.60.8620. PMID: 26101239
143. **Ballman KV**. Biomarker: Predictive or Prognostic? *J Clin Oncol*. 2015 Nov 20;33(33):3968-71. doi: 10.1200/JCO.2015.63.3651. Epub 2015 Sep 21. PubMed PMID: 26392104.
144. Zielinski MD, Kuntz MM, Polites SF, Boggust A, Nelson H, Khasawneh MA, Jenkins DH, Harmsen S, **Ballman KV**, Pieper R. A prospective analysis of urinary tract infections among elderly trauma patients. *J Trauma Acute Care Surg*. 2015 Oct;79(4):638-42. doi: 10.1097/TA.0000000000000796. PubMed PMID: 26402539; PubMed Central PMCID: PMC4582427.
145. **Ballman KV**. Biomarker-based trials in neuro-oncology. *Chin Clin Oncol*. 2015 Sep;4(3):38. doi: 10.3978/j.issn.2304-3865.2015.09.04. PubMed PMID: 26408305.
146. Perez EA, Baehner FL, Butler SM, Thompson EA, Dueck AC, Jamshidian F, Cherbavaz D, Yoshizawa C, Shak S, Kaufman PA, Davidson NE, Gralow J, Asmann YW, **Ballman KV**. The relationship between quantitative human epidermal growth factor receptor 2 gene expression by the 21-gene reverse transcriptase polymerase chain reaction assay and adjuvant trastuzumab benefit in Alliance N9831. *Breast Cancer Res*. 2015 Oct 1;17(1):133. doi: 10.1186/s13058-015-0643-7. PubMed PMID: 26429296; PubMed Central PMCID: PMC4589954.
147. Perez EA, **Ballman KV**, Tenner KS, Thompson EA, Badve SS, Bailey H, Baehner FL. Association of Stromal Tumor-Infiltrating Lymphocytes With Recurrence-Free Survival in the N9831 Adjuvant Trial in

- Patients With Early-Stage HER2-Positive Breast Cancer. *JAMA Oncol.* 2016 Jan 1;2(1):56-64. doi: 10.1001/jamaoncol.2015.3239. PubMed PMID: 26469139; PubMed Central PMCID: PMC4713247.
148. Huang RY, Rahman R, **Ballman KV**, Felten SJ, Anderson SK, Ellingson BM, Nayak L, Lee EQ, Abrey LE, Galanis E, Reardon DA, Pope WB, Cloughesy TF, Wen PY. The Impact of T2/FLAIR Evaluation per RANO Criteria on Response Assessment of Recurrent Glioblastoma Patients Treated with Bevacizumab. *Clin Cancer Res.* 2015 Oct 21. [Epub ahead of print] PubMed PMID: 26490307.
149. Park MS, Xue A, Spears GM, Halling TM, Ferrara MJ, Kuntz MM, Dhillon SK, Jenkins DH, Harmsen WS, **Ballman KV**, Harrison P, Heit JA. Thrombin generation and procoagulant microparticle profiles after acute trauma: A prospective cohort study. *J Trauma Acute Care Surg.* 2015 Nov;79(5):726-31. doi: 10.1097/TA.0000000000000839. PubMed PMID: 26496097; PubMed Central PMCID: PMC4621757.
150. Gupta SK, Kizilbash SH, Carlson BL, Mladek AC, Boakye-Agyeman F, Bakken KK, Pokorny JL, Schroeder MA, Decker PA, Cen L, Eckel-Passow JE, Sarkar G, Ballman KV, Reid JM, Jenkins RB, Verhaak RG, Sulman EP, Kitange GJ, Sarkaria JN. Delineation of MGMT Hypermethylation as a Biomarker for Veliparib-Mediated Temozolomide-Sensitizing Therapy of Glioblastoma. *J Natl Cancer Inst.* 2015 Nov 27;108(5). pii: djv369. doi: 10.1093/jnci/djv369. Print 2015 May. PubMed PMID: 26615020.
151. Boughey JC, **Ballman KV**, Le-Petross HT, McCall LM, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, Feliberti EC, Hunt KK. Identification and Resection of Clipped Node Decreases the False-negative Rate of Sentinel Lymph Node Surgery in Patients Presenting With Node-positive Breast Cancer (T0-T4, N1-N2) Who Receive Neoadjuvant Chemotherapy: Results From ACOSOG Z1071 (Alliance). *Ann Surg.* 2015 Nov 26. [Epub ahead of print] PubMed PMID: 26649589.
152. Chen J, Ryu E, Hatchcock M, **Ballman K**, Chia N, Olson JE, Nelson H. Impact of demographics on human gut microbial diversity in a US Midwest population. *PeerJ* 2016 4:e1514; DOI 10.7717/peerj.1514
153. Zielinski MD, Kuntz M, Zhang X, Zagar AE, Khasawneh MA, Zendejas B, Polites SF, Ferrara M, Harmsen WS, **Ballman KV**, Park MS, Schiller HJ, Dries D, Jenkins DH. Botulinum toxin A-induced paralysis of the lateral abdominal wall after damage-control laparotomy: A multi-institutional, prospective, randomized, placebo-controlled pilot study. *J Trauma Acute Care Surg.* 2016 Feb;80(2):237-42. doi: 10.1097/TA.0000000000000917. PMID: 26813298.
154. Haffty BG, McCall LM, **Ballman KV**, McLaughlin S, Jagsi R, Ollila DW, Hunt KK, Buchholz TA, Boughey JC. Patterns of Local-Regional Management Following Neoadjuvant Chemotherapy in Breast Cancer: Results From ACOSOG Z1071 (Alliance). *Int J Radiat Oncol Biol Phys.* 2016 Mar 1;94(3):493-502. doi: 10.1016/j.ijrobp.2015.11.005. PMID: 26867878; PMCID: PMC4752720.
155. Shoag J, Halpern JA, Lee DJ, Mittal S, **Ballman KV**, Barbieri CE, Hu JC. Decline in prostate cancer screening by primary care physicians: an analysis of trends in the use of digital rectal examination and prostate specific antigen testing. *J Urol.* 2016 Oct;196(4):1047-52. doi: 10.1016/j.juro.2016.03.171. PMID: 27060052
156. Knutson KL, Clynes R, Shreeder B, Yeramian P, Kemp K, **Ballman K**, Tenner KS, Erskine CL, Norton N, Northfelt DW, Tan W, Calfa C, Pegram MD, Mittendorf EA, Perez EA. Improved survival of HER2+ breast cancer patients treated with trastuzumab and chemotherapy is associated with host antibody immunity against the HER2 intracellular domain. *Cancer Res.* 2016 Jul 1;76(13):3702-10. PMID: 27197192
157. Nipp RD, Yao NA, Lowenstein LM, Buckner JC, Parker IR, Gajra A, Morrison VA, Dale W, **Ballman KV**. Pragmatic study designs for older adults with cancer: Report from the U13 conference. *J Geriatr Oncol.* 2016 Jul;7(4):234-41. Review. PubMed PMID: 27197914
158. Simmons RM, **Ballman KV**, Cox C, Carp N, Sabol J, Hwang RF, Attai D, Sabel M, Nathanson D, Kenler A, Gold L, Kaufman C, Han L, Bleznak A, Stanley Smith J, Holmes D, Fornage B, Le-Petross C, Hoda S, McCall L, Hunt KK; ACOSOG investigators. A Phase II Trial Exploring the Success of Cryoablation Therapy in the Treatment of Invasive Breast Carcinoma: Results from ACOSOG (Alliance) Z1072. *Ann Surg Oncol.* 2016 Aug;23(8):2438-45. PMID: 27221361
159. Osarogiagbon RU, Decker PA, **Ballman K**, Wagle D, Allen MS, Darling GE. Survival Implications of Variation in the Thoroughness of Pathologic Lymph Node Examination in American College of

- Surgeons Oncology Group Z0030 (Alliance). *Ann Thorac Surg*. 2016 Aug;102(2):363-9. PMID: 27262908
160. Park MS, Perkins SE, Spears GM, Ashrani AA, Leibson CL, Boos CM, Harmsen WS, Jenkins DH, Bailey KR, **Ballman KV**, Heit JA. Risk factors for venous thromboembolism after acute trauma: A population-based case-cohort study. *Thromb Res*. 2016 Aug;144:40-5. doi: 10.1016/j.thromres.2016.03.026. PMID: 27284980
161. Aho JM, Nourallah A, Samaha MJ, Antiel RM, Dupont SC, **Ballman KV**, Sloan JA, Bingener J. Patient-Reported Outcomes after Laparoscopic Ventral Hernia Repair. *Am Surg*. 2016 Jun;82(6):550-6. PMID: 27305889
162. Brown PD, Jaeckle K, **Ballman KV**, Farace E, Cerhan JH, Anderson SK, Carrero XW, Barker FG 2nd, Deming R, Burri SH, Ménard C, Chung C, Stieber VW, Pollock BE, Galanis E, Buckner JC, Asher AL. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. *JAMA*. 2016 Jul 26;316(4):401-9. doi: 10.1001/jama.2016.9839. PubMed PMID: 27458945.
163. Shah MV, Wiktor AE, Meyer RG, Tenner KS, **Ballman KV**, Green SJ, Sukov WR, Ketterling RP, Perez EA, Jenkins RB. Change in Pattern of HER2 Fluorescent in Situ Hybridization (FISH) Results in Breast Cancers Submitted for FISH Testing: Experience of a Reference Laboratory Using US Food and Drug Administration Criteria and American Society of Clinical Oncology and College of American Pathologists Guidelines. *J Clin Oncol*. 2016 Oct 10;34(29):3502-3510. PubMed PMID: 27458302.
164. Giuliano AE, **Ballman K**, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, Saha S, Morrow M, Hunt KK. Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases: Long-term Follow-up From the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial. *Ann Surg*. 2016 Sep;264(3):413-20. doi: 10.1097/SLA.0000000000001863.
165. Warner ET, **Ballman KV**, Strand C, Boughey JC, Buzdar AU, Carey LA, Sikov WM, Partridge AH. Impact of race, ethnicity, and BMI on achievement of pathologic complete response following neoadjuvant chemotherapy for breast cancer: a pooled analysis of four prospective Alliance clinical trials (A151426). *Breast Cancer Res Treat*. 2016 Aug;159(1):109-18. PubMed PMID: 27449492
166. Halpern JA, Shoag JE, Mittal S, Oromendia C, **Ballman KV**, Hershman DL, Wright JD, Tina Shih YC, Nguyen PL, Hu JC. Prognostic Significance of Digital Rectal Examination and Prostate Specific Antigen in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Arm. *J Urol*. 2017 Feb;197(2):363-368. doi: 10.1016/j.juro.2016.08.092. PubMed PMID: 27569432.
167. Laungani AT, Christner J, Primus JA, Lachman N, **Ballman KV**, Mohan A, Saint-Cyr M. Study of the Impact of the Location of a Perforator in the Perfusion of a Perforator Flap: The Concept of "Angle of Perfusion". *J Reconstr Microsurg*. 2017 Jan;33(1):49-58. PMID: 27636539
168. Perez EA, **Ballman KV**, Mashadi-Hosseini A, Tenner KS, Kachergus JM, Norton N, Necela BM, Carr JM, Ferree S, Perou CM, Baehner F, Cheang MC, Thompson EA. Intrinsic Subtype and Therapeutic Response Among HER2-Positive Breast Tumors from the NCCTG (Alliance) N9831 Trial. *J Natl Cancer Inst*. 2016 Oct 28;109(2). pii: djw207.
169. Halpern JA, Shoag JE, Artis AS, **Ballman KV**, Sedrakyan A, Hershman DL, Wright JD, Shih YC, Hu JC. National Trends in Prostate Biopsy and Radical Prostatectomy Volumes Following the United States Preventative Services Task Force Guidelines Against Prostate-Specific Antigen Screening. *JAMA Surg*. 2017 Feb 1;152(2):192-198. doi: 10.1001/jamasurg.2016.3987. PubMed PMID: 27806151.
170. Lewicki P, Shoag J, Golombos DM, Oromendia C, **Ballman KV**, Halpern JA, Stone BV, O'Malley P, Barbieri CE, Scherr DS. Prognostic significance of a negative prostate biopsy: An analysis of subjects enrolled in a prostate cancer screening trial. *J Urol*. 2017 Apr;197(4):1014-1019. doi: 10.1016/j.juro.2016.11.002. PubMed PMID: 27836710
171. Argenta PA, **Ballman KV**, Geller MA, Carson LF, Ghebrey R, Mullany SA, Teoh DG, Winterhoff BJ, Rivard CL, Erickson BK. The effect of photobiomodulation on chemotherapy-induced peripheral neuropathy: A randomized, sham-controlled clinical trial. *Gynecol Oncol*. 2017 Jan;144(1):159-166. doi:10.1016/j.ygyno.2016.11.013. PubMed PMID: 27887804.

172. Ashamalla H, Guirguis A, McCool K, McVorrnan S, Mattes M, Metzger D, Oromendia C, **Ballman KV**, Mokhtar B, Tchelebi M, Katsoulakis E, Raffla S. Brachytherapy improves outcomes in young men ( $\leq 60$  years) with prostate cancer: A SEER analysis. *Brachytherapy*. 2017 Jul - Aug;16(4):916-918. doi: 10.1016/j.brachy.2016.12.010. PubMed PMID: 28139417.
173. Kimmick GG, Major B, Clapp J, Sloan J, Pitcher B, **Ballman K**, Barginear M, Freedman RA, Artz A, Klepin HD, Lafky JM, Hopkins J, Winer E, Hudis C, Muss H, Cohen H, Jatoi A, Hurria A, Mandelblatt J. Using ePrognosis to estimate 2-year all-cause mortality in older women with breast cancer: Cancer and Leukemia Group B (CALGB) 49907 and 369901 (Alliance A151503). *Breast Cancer Res Treat*. 2017 Jun;163(2):391-398. doi: 10.1007/s10549-017-4188-6. PubMed PMID: 28283904.
174. Perez EA, **Ballman KV**, Mashadi-Hossein A, Tenner KS, Kachergus JM, Norton N, Necela BM, Carr JM, Ferree S, Perou CM, Baehner F, Cheang MC, Thompson EA. Intrinsic Subtype and Therapeutic Response Among HER2-Positive Breast Tumors from the NCCTG (Alliance) N9831 Trial. *J Natl Cancer Inst*. 2017 Feb 1;109(2):1-8. doi: 10.1093/jnci/djw207. PubMed PMID: 28376219.
175. Grossman SA, Schreck KC, **Ballman K**, Alexander B. Point/counterpoint: randomized versus single-arm phase II clinical trials for patients with newly diagnosed glioblastoma. *Neuro Oncol*. 2017 Apr 1;19(4):469-474. doi: 10.1093/neuonc/nox030. PubMed PMID: 28388713.
176. Reinholz MM, Chen B, Dueck AC, Tenner K, **Ballman K**, Riehle D, Jenkins RB, Geiger XJ, McCullough AE, Perez EA. IGF1R Protein Expression Is Not Associated with Differential Benefit to Concurrent Trastuzumab in Early-Stage HER2(+) Breast Cancer from the North Central Cancer Treatment Group (Alliance) Adjuvant Trastuzumab Trial N9831. *Clin Cancer Res*. 2017 Aug 1;23(15):4203-4211. doi: 10.1158/1078-0432.CCR-15-0574. PubMed PMID: 28533226.
177. Antonarakis ES, Tagawa ST, Galletti G, Worroll D, **Ballman K**, Vanhuyse M, Sonpavde G, North S, Albany C, Tsao CK, Stewart J, Zaher A, Szatrowski T, Zhou W, Gjyzezi A, Tasaki S, Portella L, Bai Y, Lannin TB, Suri S, Gruber CN, Pratt ED, Kirby BJ, Eisenberger MA, Nanus DM, Saad F, Giannakakou P; TAXYNERGY Investigators. Randomized, Noncomparative, Phase II Trial of Early Switch From Docetaxel to Cabazitaxel or Vice Versa, With Integrated Biomarker Analysis, in Men With Chemotherapy-Naïve, Metastatic, Castration-Resistant Prostate Cancer. *J Clin Oncol*. 2017 Oct 1;35(28):3181-3188. doi: 10.1200/JCO.2017.72.4138. PubMed PMID: 28632486.
178. Boughey JC, **Ballman KV**, McCall LM, Mittendorf EA, Symmans WF, Julian TB, Byrd D, Hunt KK. Tumor Biology and Response to Chemotherapy Impact Breast Cancer-specific Survival in Node-positive Breast Cancer Patients Treated With Neoadjuvant Chemotherapy: Long-term Follow-up From ACOSOG Z1071 (Alliance). *Ann Surg*. 2017 Oct;266(4):667-676. doi: 10.1097/SLA.0000000000002373. PubMed PMID: 28657941.
179. Brown PD, **Ballman KV**, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, Greenspoon J, Parney IF, Laack NNI, Ashman JB, Bahary JP, Hadjipanayis CG, Urbanic JJ, Barker FG 2nd, Farace E, Khuntia D, Giannini C, Buckner JC, Galanis E, Roberge D. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC-3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2017 Aug;18(8):1049-1060. doi: 10.1016/S1470-2045(17)30441-2. PubMed PMID: 28687377.
180. Giuliano AE, **Ballman KV**, McCall L, Beitsch PD, Brennan MB, Kelemen PR, Ollila DW, Hansen NM, Whitworth PW, Blumencranz PW, Leitch AM, Saha S, Hunt KK, Morrow M. Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial. *JAMA*. 2017 Sep 12;318(10):918-926. doi: 10.1001/jama.2017.11470. PubMed PMID: 28898379.
181. Churilla TM, **Ballman KV**, Brown PD, Twohy EL, Jaeckle K, Farace E, Cerhan JH, Anderson SK, Carrero XW, Garces YI, Barker FG 2nd, Deming R, Dixon JG, Burri SH, Chung C, Ménard C, Stieber VW, Pollock BE, Galanis E, Buckner JC, Asher AL. Stereotactic Radiosurgery With or Without Whole-Brain Radiation Therapy for Limited Brain Metastases: A Secondary Analysis of the North Central Cancer Treatment Group N0574 (Alliance) Randomized Controlled Trial. *Int J Radiat Oncol Biol Phys*. 2017 Dec 1;99(5):1173-1178. doi: 10.1016/j.ijrobp.2017.07.045. [Epub ahead of print] PubMed PMID: 28939223.
182. Galanis E, Anderson SK, Miller CR, Sarkaria JN, Jaeckle K, Buckner JC, Ligon KL, **Ballman KV**, Moore DF Jr, Nebozhyn M, Loboda A, Schiff D, Ahluwalia MS, Lee EQ, Gerstner ER, Lesser GJ, Prados M, Grossman SA, Cerhan J, Giannini C, Wen PY; Alliance for Clinical Trials in Oncology and ABTC. Phase I/II Trial of Vorinostat Combined with Temozolomide and Radiation Therapy for Newly

- Diagnosed Glioblastoma: Final Results of Alliance N0874/ABTC 02. *Neuro Oncol.* 2018 Mar 27;20(4):546-556. [Epub ahead of print] PubMed PMID: 29016887.
183. Chen J, King E, Deek R, Wei Z, Yu Y, Grill D, **Ballman K**, Stengle O. An omnibus test for differential distribution analysis of microbiome sequencing data. *Bioinformatics* 2018. 34: 643-651. doi: 10.1093/bioinformatics/btx650. PMID: 29040451
184. Gaudino M, Alexander JH, Bakaeen FG, **Ballman K**, Barili F, Calafiore AM, Davierwala P, Goldman S, Kappetein P, Lorusso R, Mylotte D, Pagano D, Ruel M, Schwann T, Suma H, Taggart DP, Tranbaugh RF, Fremes S. Randomized comparison of the clinical outcome of single versus multiple arterial grafts: the ROMA trial-rationale and study protocol. *Eur J Cardiothorac Surg.* 2017 Dec 1;52(6):1031-1040. doi: 10.1093/ejcts/ezx358. [Epub ahead of print] PubMed PMID: 29059371.
185. Halpern JA, Oromendia C, Shoag JE, Mittal S, Cosiano MF, **Ballman KV**, Vickers AJ, Hu JC. Utility of Digital Rectal Examination (DRE) as an Adjunct to Prostate Specific Antigen (PSA) in the Detection of Clinically Significant Prostate Cancer. *J Urol.* 2018 Apr;199(4):947-953. doi: 10.1016/j.juro.2017.10.021. [Epub ahead of print] PubMed PMID: 29061540.
186. Le-Petross HT, McCall LM, Hunt KK, Mittendorf EA, Ahrendt GM, Wilke LG, **Ballman KV**, Boughey JC. Axillary Ultrasound Identifies Residual Nodal Disease After Chemotherapy: Results From the American College of Surgeons Oncology Group Z1071 Trial (Alliance). *AJR Am J Roentgenol.* 2018 Jan 30;1-8. doi: 10.2214/AJR.17.18295. [Epub ahead of print] PubMed PMID: 29381381.
187. Chen J, Oromendia C, Halpern JA, **Ballman KV**. National trends in management of localized prostate cancer: A population based analysis 2004-2013. *Prostate.* 2018; 78(7):512-520. doi: 10.1002/pros.23496. [Epub ahead of print] PubMed PMID: 29542178.
188. Gajra A, McCall L, Muss HB, Cohen HJ, Jatoi A, **Ballman KV**, Partridge AH, Sutton L, Parker BA, Magrinat G, Klepin HD, Lafky JM, Hurria A. The preference to receive chemotherapy and cancer-related outcomes in older adults with breast cancer CALGB 49907 (alliance). *J Geriatr Oncol.* 2018; 9(3):221-227. doi: 10.1016/j.jgo.2018.02.003. [Epub ahead of print] PubMed PMID: 29602735.
189. Schumacher JR, Neuman HB, Chang GJ, Kozower BD, Edge SB, Yu M, Vanness DJ, Si Y, Jacobs EA, Francescatti AB, Spears PA, Havlena J, Adesoye T, McKellar D, Winchester D, Burnside ES, Greenberg CC; Alliance ACS-CRP CCDR Breast Cancer Surveillance Working Group. A National Study of the Use of Asymptomatic Systemic Imaging for Surveillance Following Breast Cancer Treatment (AFT-01). *Ann Surg Oncol.* 2018; 25(9):2587-2595. doi: 10.1245/s10434-018-6496-4. PubMed PMID: 29777402.
190. Díaz I, Savenkov O, **Ballman K**; Targeted learning ensembles for optimal individualized treatment rules with time-to-event outcomes, *Biometrika*, asy017, <https://doi.org/10.1093/biomet/asy017>
191. Li D, McCall LM, Hahn OM, Hudis CA, Cohen HJ, Muss HB, Jatoi A, Lafky JM, **Ballman KV**, Winer EP, Tripathy D, Schneider B, Barry W, Dickler MN, Hurria A. Identification of risk factors for toxicity in patients with hormone receptor-positive advanced breast cancer treated with bevacizumab plus letrozole: a CALGB 40503 (alliance) correlative study. *Breast Cancer Res Treat.* 2018 171(2):325-334. doi: 10.1007/s10549-018-4828-5. PubMed PMID: 29789969.
192. Schumacher JR, Neuman HB, Chang GJ, Kozower BD, Edge SB, Yu M, Vanness DJ, Si Y, Jacobs EA, Francescatti AB, Spears PA, Havlena J, Adesoye T, McKellar D, Winchester D, Burnside ES, Greenberg CC; Alliance ACS-CRP CCDR Breast Cancer Surveillance Working Group. A National Study of the Use of Asymptomatic Systemic Imaging for Surveillance Following Breast Cancer Treatment (AFT-01). *Ann Surg Oncol.* 2018 May 17. doi: 10.1245/s10434-018-6496-4. [Epub ahead of print] PubMed PMID: 29777402.
193. Li D, McCall LM, Hahn OM, Hudis CA, Cohen HJ, Muss HB, Jatoi A, Lafky JM, **Ballman KV**, Winer EP, Tripathy D, Schneider B, Barry W, Dickler MN, Hurria A. Identification of risk factors for toxicity in patients with hormone receptor-positive advanced breast cancer treated with bevacizumab plus letrozole: a CALGB 40503 (alliance) correlative study. *Breast Cancer Res Treat.* 2018;171(2):325-334. doi: 10.1007/s10549-018-4828-5. Epub 2018 May 22. PMID: 29789969
194. Norton N, Fox N, McCarl CA, Tenner KS, **Ballman K**, Erskine CL, Necela BM, Northfelt D, Tan WW, Calfa C, Pegram M, Colon-Otero G, Perez EA, Clynes R, Knutson KL. Generation of HER2-specific antibody immunity during trastuzumab adjuvant therapy associates with reduced relapse in resected HER2 breast cancer. *Breast Cancer Res.* 2018 Jun 14;20(1):52. doi: 10.1186/s13058-018-0989-8. PubMed PMID: 29898752.

195. Armer JM, **Ballman KV**, McCall L, Armer NC, Sun Y, Udmuangpia T, Hunt KK, Mittendorf EA, Byrd DR, Julian TB, Boughey JC. Lymphedema symptoms and limb measurement changes in breast cancer survivors treated with neoadjuvant chemotherapy and axillary dissection: results of American College of Surgeons Oncology Group (ACOSOG) Z1071 (Alliance) substudy. *Support Care Cancer*. 2019 Feb;27(2):495-503. doi: 10.1007/s00520-018-4334-7. [Epub ahead of print] PubMed PMID: 29980907
196. Rosenkranz KM, **Ballman K**, McCall L, Kubicky C, Cuttino L, Le-Petross H, Hunt KK, Giuliano A, Van Zee KJ, Haffty B, Boughey JC. The Feasibility of Breast-Conserving Surgery for Multiple Ipsilateral Breast Cancer: An Initial Report from ACOSOG Z11102 (Alliance) Trial. *Ann Surg Oncol*. 2018 Oct;25(10):2858-2866. doi: 10.1245/s10434-018-6583-6. [Epub ahead of print] PubMed PMID: 29987605.
197. Desai P, Mencia-Trinchant N, Savenkov O, Simon MS, Cheang G, Lee S, Samuel M, Ritchie EK, Guzman ML, **Ballman KV**, Roboz GJ, Hassane DC. Somatic mutation precede acute myeloid leukemia years before diagnosis. *Nat Med*. 2018 Jul;24(7):1015-1023. doi: 10.1038/s41591-018-0081-z. Epub 2018 Jul 9. PubMed PMID: 29988143.
198. Ma KC, Schenck EJ, Siempos II, Cloonan SM, Finkelstein EJ, Pabon MA, Oromendia C, **Ballman KV**, Baron RM, Fredenburgh LE, Higuera A, Lee JY, Chung CR, Jeon K, Yang JH, Howrylak JA, Huh JW, Suh GY, Choi AM. Circulating RIPK3 levels are associated with mortality and organ failure during critical illness. *JCI Insight*. 2018 Jul 12;3(13). pii: 99692. doi: 10.1172/jci.insight.99692. [Epub ahead of print] PubMed PMID: 29997296.
199. Hurria A, Soto-Perez-de-Celis E, Allred JB, Cohen HJ, Arsenyan A, **Ballman K**, Le-Rademacher J, Jatoi A, Filo J, Mandelblatt J, Lafky JM, Kimmick G, Klepin HD, Freedman RA, Burstein H, Gralow J, Wolff AC, Magrinat G, Barginear M, Muss H. Functional Decline and Resilience in Older Women Receiving Adjuvant Chemotherapy for Breast Cancer. *J Am Geriatr Soc*. 2018 Aug 26. doi: 10.1111/jgs.15493. [Epub ahead of print] PubMed PMID: 30146695.
200. Beltran H, Oromendia C, Danila DC, Montgomery B, Hoimes C, Szmulewitz RZ, Vaishampayan U, Armstrong AJ, Stein M, Pinski J, Mosquera JM, Sailer V, Bareja R, Romanel A, Gumpeni N, Sboner A, Dardenne E, Puca L, Prandi D, Rubin MA, Scher HI, Rickman DS, Demichelis F, Nanus DM, **Ballman KV**, Tagawa ST. A phase II trial of the aurora kinase A inhibitor alisertib for patients with castration resistant and neuroendocrine prostate cancer: efficacy and biomarkers. *Clin Cancer Res*. 2019 Jan 1;25(1):43-51. pii: clincanres.1912.2018. doi: 10.1158/1078-0432.CCR-18-1912. PubMed PMID: 30232224.
201. Yu H, Chen Z, **Ballman K**, Watson MA, Govindan R, Lanc I, Beer DG, Bueno R, Chirieac L, Chui MH, Chen G, Franklin WA, Gandara DR, Genova C, Brovsky K, Harpole D, Joshi M, Merrick DT, Richards W, Rivard CJ, Tsao MS, van Bokhoven A, Shepherd FA, Hirsch FR. Correlation of PD-L1 expression with tumor mutation burden and gene signatures for prognosis in early stage squamous cell lung carcinoma. *J Thorac Oncol*. 2019 Jan;14(1):25-36. pii: S1556-0864(18)33116-2. doi: 10.1016/j.jtho.2018.09.006. PubMed PMID: 30253973.
202. Tagawa ST, Antonarakis ES, Gjyrezi A, Galletti G, Kim S, Worroll D, Stewart J, Zaher A, Szatrowski TP, **Ballman KV**, Kita K, Tasaki S, Bai Y, Portella L, Kirby BJ, Saad F, Eisenberger MA, Nanus DM, Giannakakou P. Expression of AR-V7 and ARv567es in circulating tumor cells correlates with outcomes to taxane therapy in men with metastatic prostate cancer treated in TAXYNERGY. *Clin Cancer Res*. 2018 Oct 9. pii: clincanres.0320.2018. doi: 10.1158/1078-0432.CCR-18-0320. [Epub ahead of print] PubMed PMID: 30301829.
203. Choy E, **Ballman K**, Chen J, Dickson MA, Chugh R, George S, Okuno S, Pollock R, Patel RM, Hoering A, Patel S. SARC018\_SPORE02: Phase II Study of Mocetinostat Administered with Gemcitabine for Patients with Metastatic Leiomyosarcoma with Progression or Relapse following Prior Treatment with Gemcitabine-Containing Therapy. *Sarcoma*. 2018 Oct 24;2018:2068517. doi: 10.1155/2018/2068517. eCollection 2018. PubMed PMID: 30473623; PubMed Central PMCID: PMC6220374.

## 2. Editorials and Letters

1. Ellis M, **Ballman K**. Trawling for genes that predict response to breast cancer adjuvant therapy. *J Clin Oncol*. 2004 Jun 15; 22(12):2267-9. (Editorial) PMID:15136594.

2. Goodwin PJ, **Ballman KV**, Small EJ, Cannistra SA. Evaluation of treatment benefit in Journal of Clinical Oncology. J Clin Oncol. 2013 Mar 20; 31(9):1123-4. Epub 2013 Jan 28. PMID:23358984. DOI:10.1200/JCO.2012.47.6952. (Editorial)
3. Sleijfer S, **Ballman K**, Verweij J. The future of drug development? Seeking evidence of activity of novel drugs in small groups of patients. J Clin Oncol. 2013 Jun 20; 31(18):2246-8. Epub 2013 Apr 29. PMID:23630203. DOI:10.1200/JCO.2013.48.7645. (Editorial)
4. Nelson H, **Ballman K**. Achieving the right volume of randomized controlled trials. Ann Surg. 2013 Aug; 258(2):208-9. PMID:23751450. DOI:10.1097/SLA.0b013e31829c4a05. (Editorial)
5. **Ballman KV**. Phase I trial improvement: a question of patient selection, trial design, or both? J Clin Oncol. 2014 Feb 20; 32(6):489-90. Epub 2014 Jan 13. PMID:24419111. DOI:10.1200/JCO.2013.53.6896. (Editorial)
6. Goodwin PJ, **Ballman KV**, Levine M. Twenty-twenty hindsight: an adjuvant breast cancer trial through the retrospectroscope. J Clin Oncol. 2014 Aug 1; 32(22):2284-6. Epub 2014 Jun 16. PMID:24934788. DOI:10.1200/JCO.2014.55.9344. (Editorial)
7. Connolly HM, **Ballman KV**, Roger VL, Tajik AJ. Aortic stenosis: no more hemodynamic cardiac catheterization! Mayo Clin Proc. 2001 Sep; 76(9):961. PMID:11560311. DOI:10.4065/76.9.961. (Letter)
8. Cooper LT, Tse TS, Mikhail MA, McBane RD, Stanson AW, **Ballman KV**. Long-term survival and amputation risk in Thromboangiitis obliterans (Buerger's disease). J Am Coll Cardiol. 2004 Dec 21; 44(12):2410-1. PMID:15607407. (Letter)
9. Giuliano AE, Morrow M, **Ballman KV**. Axillary vs sentinel lymph node dissection for invasive breast cancer. JAMA. 2011 Jun 8; 305(22):2290-1. (Letter)
10. Goodwin PJ, **Ballman KV**, Small EJ, Levine M, Cannistra SA. Evaluation of treatment benefit: randomized controlled trials and population-based observational research reply. J Clin Oncol. 2013 Sep 10; 31(26):3300. (Letter)
11. **Ballman KV**, Mauer M, Wedding U, Mohile SG, Muss H, Extermann M, Luciani A, Cohen HJ, Hurria A, Lichtman SM, Curigliano G, Wildiers H. Reply to L.K. Mell et al. J Clin Oncol. 2014 Apr 1; 32(10):1090-1. Epub 2014 Feb 18. PMID:24550420. DOI:10.1200/JCO.2013.54.5236. (Letter)
12. **Ballman KV**. Reply to D.M. Hyman et al and M. Voskoboynik et al. J Clin Oncol. 2014 Oct 1; 32(28):3200. Epub 2014 Jul 28. PMID:25071106. DOI:10.1200/JCO.2014.56.5770. (Letter)
13. **Ballman KV**. Surprising results from an angiotensin-converting enzyme inhibitor trial in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2016; 194(11):1307-1308.
14. **Ballman KV**, McCall LM, Giuliano AE. Axillary vs Sentinel Lymph Node Dissection in Women With Invasive Breast Cancer-Reply. JAMA. 2018 Jan 16;319(3):306-307. doi: 10.1001/jama.2017.18318. PubMed PMID: 29340672.
15. Rosenkranz KM, **Ballman K**, McCall L, Kubicky CD, Cuttino L, Le-Petross H, Hunt K, Giuliano A, Van Zee K, Haffty B, Boughiey J. Reply to "Can Patients with Multiple Breast Cancers in the Same Breast Avoid Mastectomy by Having Multiple Lumpectomies to Achieve Equivalent Rates of Local Breast Cancer Recurrence? Response to the Preliminary Alliance 11102 Trial Report". Ann Surg Oncol. 2019. Feb;26(2):702. doi: 10.1245/s10434-018-6984-6. Epub 2018 Dec 12. PubMed PMID: 30542836.

### 3. Chapters

1. **Ballman KV**, Votta L. Organizational congestion in large-scale software development. Proceedings of the Third International Conference on Software Process, 1994.
2. **Ballman KV**. Real Data in Classroom Examples. In: Teaching Resources for Undergraduate Statistics. 2000. (Book chapter)
3. **Ballman KV**. Handbook of Clinical Cancer Research. Springer 2018. (Book chapter)
4. **Ballman KV**. Predictive Biomarkers in Oncology. Springer 2019. (Book chapter)

# EXHIBIT B

List of Testimony Given in the Last Four Years by Karla V. Ballman, Ph.D.

**Depositions**

**July 21, 2017**

*BTG International Ltd. v. Actavis Laboratories Fl., Inc.*, No. 2:16-cv-05909-KM-JBC,  
U.S. District Court for the District of New Jersey

AND

*BTG International Ltd. v. Amerigen Pharmaceuticals, Inc.*, No. 2:16-cv-02449-KM-JBC,  
U.S. District Court for the District of New Jersey

**Oct. 30, 2018**

*In re: Viagra (Sildenafil Citrate) and Cialis (Tadalafil) Products Liability Litigation*, No.  
3:16-md-02691, MDL No. 2691, U.S. District Court for the Northern District of  
California (San Francisco Division)

**Trial Testimony**

**July 26, 2017**

*BTG International Ltd. v. Actavis Laboratories Fl., Inc.*, No. 2:16-cv-05909-KM-JBC,  
U.S. District Court for the District of New Jersey

AND

*BTG International Ltd. v. Amerigen Pharmaceuticals, Inc.*, No. 2:16-cv-02449-KM-JBC,  
U.S. District Court for the District of New Jersey

# Exhibit 148

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

**IN RE: JOHNSON & JOHNSON TALCUM  
POWDER PRODUCTS MARKETING, SALES  
PRACTICES AND PRODUCTS LIABILITY  
LITIGATION**

**MDL NO. 16-2738 (FLW) (LHG)**

***THIS DOCUMENT RELATES TO ALL CASES***

**EXPERT REPORT OF CHRISTIAN MERLO, MD, MPH  
FOR GENERAL CAUSATION *DAUBERT* HEARING**

Date: February 25, 2019



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Christian Merlo, M.D., M.P.H.

## **I. SCOPE OF REPORT**

I was asked to address fundamental tenets of epidemiology, to review the epidemiology related to the potential association between perineal talc use and ovarian cancer, to review plaintiffs' epidemiology experts' reports, and to offer my opinions on their methodologies.

All of the opinions in this report are stated to a reasonable degree of scientific certainty.

I am being compensated at a rate of \$530 per hour for record review and drafting my report and \$720 per hour for testimony.

My curriculum vitae, a list of literature that I have reviewed, and a list of testimony I have provided in the last four years may be found in Appendices A, B and C.

## **II. PROFESSIONAL QUALIFICATIONS**

My name is Christian Merlo. I am a licensed physician in the state of Maryland and am board certified in internal medicine, pulmonary medicine and critical care medicine. I am an attending physician at the Johns Hopkins Hospital and the Johns Hopkins Bayview Medical Center and care for patients both in the hospital and in our outpatient centers. I am Associate Professor of Medicine in the Division of Pulmonary and Critical Care Medicine at the Johns Hopkins University School of Medicine, and in addition, I am Associate Professor of Epidemiology in the Department of Epidemiology at the Johns Hopkins Bloomberg School of Public Health. I am also a member of the *Alpha Omega Alpha* honor society for medicine.

I have provided patient care and consultation as a clinical physician and have taught medicine in the fields of general medicine, pulmonary medicine and critical care medicine for more than 18 years.

I received my doctorate in medicine at Georgetown University School of Medicine and completed my residency in internal medicine at Georgetown University Medical Center, where I also served as Chief Resident. I completed a four-year fellowship in Pulmonary and Critical Care Medicine at the Johns Hopkins Hospital, and during this period in time, I also received a master's degree in public health from the Johns Hopkins Bloomberg School of Public Health.

I was offered a faculty position in 2004 as Instructor in Medicine at the Johns Hopkins University School of Medicine, and was promoted to Assistant Professor of Medicine in 2006. In 2009, I was awarded a joint faculty appointment as Assistant Professor of Epidemiology at the Johns Hopkins Bloomberg School of Public Health, and in 2015, I was promoted to Associate Professor of Medicine and Epidemiology.

I am the Associate Program Director of the Adult Cystic Fibrosis Program at the Johns Hopkins Cystic Fibrosis Center, one of the largest cystic fibrosis centers in the country, and in addition, I am the Director of Research for both the Adult Cystic Fibrosis Program and the Lung Transplant Program at the Johns Hopkins Hospital. I am also an Associate Program Director for Research and Scholarship for the Osler Medical Residency

program. I have specific expertise in the clinical care of patients with cystic fibrosis and those who undergo lung transplantation, as well as in the care of patients with other pulmonary diseases or those that require critical care therapies. My research involves the design of clinical studies investigating the impact of environmental and infectious exposures on outcomes for patients with cystic fibrosis and those who undergo lung transplantation.

I am currently principal investigator or co-investigator on many NIH-funded and pharmaceutical industry-sponsored clinical trials. I have authored or co-authored more than 70 manuscripts, book chapters and commentaries on topics involving cystic fibrosis and lung transplantation, as well as on topics in general pulmonary medicine and critical care medicine. As a clinical investigator, I have had rigorous training and have expertise in clinical epidemiology, with specific training in clinical trial design, conduct and analysis. My ties with the School of Public Health have provided ongoing collaboration to help research the epidemiologic nature of the exposure/outcome causal pathway in diseases involving internal medicine, pulmonary medicine and critical care medicine.

I am also an expert in the methodologic approach to the study of disease and have more than 15 years of experience teaching coursework on study design and analysis, as well as conducting research on the epidemiologic nature of the exposure/outcome relationship with a strong command of the strengths and limitations of epidemiologic investigation.

### **III. FUNDAMENTAL PRINCIPLES OF EPIDEMIOLOGY**

Although there are many definitions of epidemiology, a widely accepted definition describes epidemiology as:

*the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems.*<sup>1</sup>

Epidemiology is a scientific discipline that relies heavily on an unbiased approach to the collection, analysis and interpretation of data. Epidemiology places an emphasis on the frequency and rate of health events as well as how personal characteristics such as demographics, socioeconomic status, behaviors and environmental exposures play a role in health-related events. Epidemiology is a science, and epidemiologic studies, when designed, conducted, analyzed and interpreted appropriately, can be powerful tools in the critical examination of the causal pathway between exposure and outcome.

#### ***A. Fundamentals Of Epidemiologic Study Design***

Researchers often have to choose a study design based on the research question, as not all study designs are appropriate for all questions. Many research questions are suitable to be answered using a classic experimental design such as the randomized controlled trial. For instance, it may be appropriate to use a randomized controlled trial design to investigate

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<sup>1</sup> See, e.g., Centers for Disease Control & Prevention, Principles of Epidemiology in Public Health Practice, Third Edition, An Introduction to Applied Epidemiology and Biostatistics, Lesson 1: Introduction to Epidemiology, <https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section1.html> (footnote omitted).

the effect of a new cholesterol lowering agent on mortality in patients with heart disease. An example of this is the Scandinavian Simvastatin Survival Study,<sup>2</sup> in which researchers studied 4,444 patients with heart disease who were either treated with simvastatin or placebo. The investigators found a significant reduction in the risk of death from heart disease in the simvastatin group compared to placebo.

Other research questions are not suitable for an experimental design in humans because of the potential for harm, lack of equipoise or ethical concerns. One such example is the effect of cigarette smoking on risk of death and risk of death from lung cancer. In order to attempt to answer this, researchers would not be able to use an experimental design, and more likely would have to use an observational study design. Doll and Hill<sup>3</sup> sent out a short but detailed questionnaire asking more than 59,000 British physicians about smoking habits and obtained follow-up information regarding mortality and lung cancer risk. In this very large observation cohort, Doll and Hill were able to demonstrate a significant increase in all-cause mortality as well as deaths due to lung cancer among cigarette smokers when compared to non-smokers.

Sometimes, the experimental study design is appropriate, and other times, an observational study design is necessary, but it is only with careful and detailed attention to the study design (study type, study size, exposure assessment, attempt to limit bias and confounding), conduct and analysis that the cause of disease can possibly be determined.

### ***B. Limitations Of Epidemiologic Study Design***

All epidemiologic studies have the advantage and limitation of studying humans rather than experimental animals. Each epidemiologic study design (detailed in the **STUDY DESIGN CONSIDERATIONS** section), however, not only has its strengths, but also weaknesses.

For example, consider the design of an epidemiologic study to evaluate the question:

*“Does regular aerobic exercise decrease the risk of heart disease?”*

A randomized controlled trial, one might think, would be the most rigorous approach and the method most similar to a laboratory scientist working in a highly controlled environment with experimental animals. Suppose researchers choose a group of subjects who don’t exercise regularly, divide the group randomly into an intervention group, who are instructed to perform aerobic exercise for 30 minutes three times a week, and a control group, who are instructed to continue with a low exercise lifestyle. The investigators will follow both groups looking for signs of heart disease, and if they are correct, subjects who exercise will get less heart disease. With this study design there may be a problem with controlling how much the subjects exercise. In the laboratory, a scientist can control exactly how much an experimental animal exercises, but in the real world this

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<sup>2</sup> The Scandinavian Simvastatin Survival Study Group, *Design and baseline results of the Scandinavian Simvastatin Survival Study of patients with stable angina and/or previous myocardial infarction*. (1993) 71 Am J Cardiol 393.

<sup>3</sup> Doll & Hill, *The mortality of doctors in relation to their smoking habits*. (1954) 328 (7455) BMJ. 1529 .

may be difficult to control. The intervention group may become lazy and not exercise, while the control group might have concern about heart disease and increase exercise, which would affect the study results.

The researchers might attempt a cohort study and follow a large group of people without heart disease over a period of time and ask them detailed questions about exercise and then after several years compare the rate of heart disease among those who exercise regularly to those who do not. Again, if the researchers are correct, patients who exercise regularly will develop less heart disease. One potential problem with this design is that people who exercise regularly may differ in other ways from people who do not exercise regularly. For example, the people who exercise regularly might be more likely to eat healthier and less likely to smoke and have a reduced risk of heart disease that is unrelated to exercise.

The researchers might also choose to perform a case-control study and identify a group of people with heart disease from the hospital coronary care unit as well as a comparable group from the hospital without heart disease. The investigators would then question both groups about their exercise over the past several years and classify each as either exercising regularly or not exercising regularly. Once again, if the researchers are correct, the patients with heart disease will report less exercise than controls. One potential problem with this approach is that people may not be able to remember their exercise patterns, or those with heart disease might feel self-conscious about reporting true exercise patterns and the information obtained about the exposure may not be reliable.

#### **IV. EVALUATING THE ACCURACY OF EPIDEMIOLOGIC STUDIES**

##### ***A. Accuracy Of An Epidemiologic Study***

In an ideal setting, all epidemiologic studies would be designed, conducted, analyzed, and interpreted in a fashion that eliminated sources of error. One of the major goals for epidemiologists is to minimize error as much as possible. Similarly, it is important for those who read and use the epidemiologic literature to be cautious in how the information is interpreted. As such, it is important to understand the factors that can influence the accuracy of epidemiologic study as errors can arise from three main sources – bias, confounding and random error.

Accuracy requires both validity and precision. Bias and confounding affect the validity of a study, while random error affects the precision of a study.

##### ***B. Validity***

Validity of epidemiologic studies is defined as the “degree to which inferences are warranted given the methods and study population chosen.”<sup>4</sup> There are two major types of validity – internal validity and external validity. Internal validity represents how well the study findings, aside from random error, represent the truth in the population being studied. The internal validity of an epidemiologic study can be challenged by systematic error caused by either or both of bias and confounding. This systematic error in the study design, conduct, analysis or interpretation can lead to either artificial elevation or artificial

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<sup>4</sup> Oleckno, *Epidemiology: Concepts & Methods* (2008).

reduction in the measures of association between exposure and outcome. External validity, sometimes referred to as generalizability, is the extent to which the results of the study can be applied to populations other than the population under investigation. It is often felt that internal validity is more important than external validity because if a study is not valid, then why would one generalize a non-internally-valid study to another population. The above-mentioned Scandinavian Simvastatin Survival Study<sup>5</sup> results were believed to be internally valid, and it was also felt to be reasonable to apply these results to other populations.<sup>6</sup>

### **C. Bias**

Bias is a type of systematic non-random error in the design and/or conduct of an epidemiologic study. Bias can have a dramatic effect on the internal validity of a study and because of this, can affect the accuracy of the study. In general, bias can be broken down into two main categories, known as selection bias and information bias. Both of these types of bias can lead to either an overestimation or underestimation of risk in epidemiologic studies. Although bias can be present in all types of studies, bias can be a particularly significant concern in observational studies, especially in those studies that are poorly designed.

Selection bias refers to a systematic error due to the way in which subjects are selected for the study. This type of bias can occur when the subjects in the study population differ from the subjects in the source population. This can occur in a cross-sectional or case-control study when the frequency of the exposure or outcome differs systematically between the study population and the source population. Because of this, selection bias can sometimes lead to an association when one does not actually exist. For instance, an investigator interested in researching whether coffee drinking is associated with a specific type of cancer designs a case-control study and obtains cases from an oncology clinic. The investigator obtains controls from a nearby heartburn clinic. The study is performed, and the investigator finds that coffee drinkers are 1.5 times more likely to develop a specific type of cancer. Since controls are recruited from a different clinic than the cases, it is possible that controls may be systematically different from cases in a way that may affect the study results. In fact, since controls were recruited from a nearby heartburn clinic where patients are routinely instructed to reduce or stop coffee drinking, controls are less likely to be coffee drinkers than all people who would be eligible controls and lead to an overestimate of risk due to selection bias.

Information bias refers to a systematic error due to measurement errors that leads to misclassification of study subjects with regards to either exposure or outcome. Information bias tends to occur during the data collection portion of an epidemiologic study. This misclassification of either exposure or outcome can be characterized as either differential or nondifferential. Differential misclassification can occur when the likelihood of misclassification is different between the study and comparison groups. Differential misclassification may lead to either overestimation or underestimation of the true value of the measure of association. If the cases in a case-control study are more likely to be

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<sup>5</sup> The Scandinavian Simvastatin Survival Study Group. *Design and baseline results of the Scandinavian Simvastatin Survival Study of patients with stable angina and/or previous myocardial infarction.* (1993) 71 Am J Cardiol 393.

<sup>6</sup> *Id.*

misclassified as exposed than the controls, then the study will tend to overestimate the true estimate of risk (odds ratio).

For example, suppose an investigator is interested in studying whether high blood pressure is associated with drinking sugary drinks. A case-control study is designed, and the investigator finds 200 cases with high blood pressure and 200 controls with normal blood pressure. The investigator then asks questions about sugary drink habits during the previous five years. The responses are collected and analyzed (table a), and there is a statistically significant increase in risk of high blood pressure with drinking sugary drinks (OR: 3.67;  $p < 0.001$ ), suggesting sugary drinks are associated with high blood pressure. If cases are systematically more likely to report sugary drink usage than controls (differential misclassification because of the belief that sugary drinks may cause high blood pressure), then this will lead to an overestimation of the true estimate of risk. In reality, if there was no increase (table b) in reporting sugary drink consumption among cases (no misclassification), there would be a non-statistically significant estimate of risk (OR: 1.35;  $p = 0.13$ ).

a.

	Study			
	High BP	No high BP		
Sugary drinks	150	90	OR=3.67	P<0.001
No sugary drinks	50	110		
	200	200		

b.

	Truth			
	High BP	No high BP		
Sugary drinks	105	90	OR=1.35	P=0.13
No sugary drinks	95	110		
	200	200		

Nondifferential misclassification can occur when there is likely an equal proportion of misclassification of exposure status among those with and without an outcome or of outcome status among those with and without an exposure. This type of misclassification typically results in a dilution of the effect of exposure on outcome and is more likely to result in no association when an association between exposure and outcome actually exists.

One specific type of bias that leads to misclassification and that is common in case-control studies is known as recall bias. It often results from the fact that cases tend to remember past exposures more than controls. It may also arise if cases are more likely than controls to investigate whether certain risk factors increase the risk of developing a certain disease. Recall bias is often less likely to occur when both cases and controls are patients, for example, in hospitalized patients,<sup>7</sup> where the degree of thinking about a possible exposure or outcome is likely to be at similar levels. Consider again the above example of the investigator who is trying to determine if there is a relationship between sugary drinks and high blood pressure. If the cases tend to recall and report more sugary drink consumption simply because they have reflected more on their past experiences, recall bias

<sup>7</sup> Schultz & Grimes, *Case-control studies: research in reverse*. (2002) 359(9304) Lancet 431; Schlesselman, *Case-control studies: design, conduct, analysis* (1982).

could result in an overestimation of the measure of risk between the sugary drinks and high blood pressure.

As particularly pertinent here, in one case-control study involving the potential association between perineal talc use and ovarian cancer,<sup>8</sup> the investigators examined whether cases and controls reported talc use more frequently if they were interviewed after 2014, which is the year when two widely publicized lawsuits concerning talc use were filed, as opposed to before that year. For those interviewed prior to 2014, approximately the same percentage of cases and controls reported genital talc use (36.5% for cases, 34.0% for controls). For those interviewed after 2014, cases reported talc use 51.5% of the time, while the percentage of controls reporting talc use remained about the same (34.4%). This is a clear demonstration of the effect of recall bias in case-control studies. Critically, that study found a statistically significant risk of ovarian cancer for those who were interviewed after 2014 at 2.91 (95% CI: 1.70-4.97). For those interviewed prior to 2014, no statistically significant association was found.<sup>9</sup> As discussed in Section VIII.B below, such concerns of recall bias could have affected pre-2014 studies as well.

Selection and information bias can best be controlled and prevented during the design and conduct of a study. This means that investigators must recognize the potential sources of bias and take precautions to minimize this bias. Methods have been developed to prevent or minimize bias in epidemiologic studies. Some of these include attempts to standardize data collection, pilot test data collection instruments, use objective methods to measure exposure and outcome status, verify subject response from other sources and obtain multiple measurements of exposure and outcome status.

#### ***D. Confounding***

In epidemiology, confounding is a misrepresentation of the true effect of an exposure on an outcome due to an association between the exposure and another factor. This factor is often referred to as a confounder, and like bias, confounding is a systematic, non-random error that can affect the internal validity of a study. Confounding can result in an overestimation or underestimation of the true effect of an exposure on an outcome. In general, for another factor to confound the effect of an exposure on the outcome, three conditions must be met: (1) the factor must be associated with the exposure; (2) the factor must be associated with the outcome; and (3) the factor must not represent a step in the causal pathway between exposure and outcome. Many times, epidemiologists do not know what extra factors will confound an actual effect of an exposure on an outcome, but it is important for suspected factors to be considered as potential confounders. Experienced epidemiologists are usually able to anticipate suspected confounders given previous experience in similar studies or based on previous studies looking at a similar exposure outcome relationship.

The Sister Study, which I discuss in more detail below, is one example of potential confounding affecting the measurement of the effect of genital talc exposure.<sup>10</sup> In that

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<sup>8</sup> Schildkraut et al., *Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)*. (2016) 25(10) Cancer Epidemiol Biomarkers Prev. 1411.

<sup>9</sup> *Id.*

<sup>10</sup> Gonzalez et al., *Douching, Talc Use, and Risk of Ovarian Cancer*. (2016) 27 Epidemiology 797.

study, in addition to talc use, participants were also asked about their douching habits. Of the 50,884 women who completed questionnaires, 154 women developed ovarian cancer. Ever douching during the 12 months prior to the study was associated with a statistically significant risk of ovarian cancer (HR: 1.8; 95% CI: 1.2-2.8) when compared with never douching after adjusting for confounders.<sup>11</sup> In contrast, there was no statistically significant increase risk of ovarian cancer (HR: 0.73; 95% CI: 0.44-1.2) with ever talc use during the 12 months prior to the study when compared with never talc use after adjusting for confounders.<sup>12</sup> There was no change in the estimated effect of talc use after adjustment for douching, and similarly, there was no change in the estimated effect of douching after adjusting for talc use. If those who use talc are more likely to douche, as is demonstrated in this and other studies,<sup>13</sup> and douching has a significant effect on the risk of ovarian cancer in this study, prior studies that have revealed a significant effect of talc on ovarian cancer may have been confounded by douching.

Although the amount of confounding is the degree to which the measure of association is affected, it is not appropriate to evaluate confounding using statistical tests of significance. In order to ensure the validity of an epidemiologic study, all attempts should be made to control confounding. While bias usually occurs in the study design and data collection phases of an epidemiologic study, confounding usually occurs during the design and analysis phases. Epidemiologists can work to control confounding in the design phase by restricting subjects to only certain characteristics, matching to attempt to create study and comparison groups that are similar with respect to potential confounders, and randomization to decrease confounding by increasing the likelihood that the study group is similar to the comparison group with regard to known factors, as well as unknown potential confounders.

#### ***E. Precision***

Precision is a measure of the amount of nonsystematic or random error that is present in the study. Random error is variability in a measure that is simply due to chance, and it represents unexplained error in a study. In epidemiologic studies, a precise result would be very easily replicated. Random errors tend to cause inconsistency between different studies and may make it less likely that investigators will find an association between exposure and outcome.

#### ***F. Random Error***

Random error affects the precision (and thus, the accuracy) of an epidemiologic study. Measurement error and sampling variation are the two main components of random error. Measurement error occurs because of an error in the measuring of the value of a variable. This may be the result of inaccurate measuring devices or due to the subjective type of some exposures or outcomes. Measurement error can be minimized by taking multiple measurements for a certain exposure or outcome. For instance, assume the above case-control study designed to investigate the effect of sugary drinks on blood pressure.

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<sup>11</sup> *Id.*

<sup>12</sup> *Id.*

<sup>13</sup> Rosenblatt et al., *Characteristics of women who use perineal powders*. (1998) 92(5) *Obstet Gynecol* 753.

Investigators might consider taking several measures of blood pressure and using the average to minimize measurement error. A second form of random error, sampling variation, can occur because samples used in an epidemiologic study are only estimates of the desired population of interest to study. Consider again the above case-control study in which investigators report the odds ratio of 1.35 as the risk estimate of the effect of sugary drinks on high blood pressure. Suppose the investigators replicated the study using a new sample of the same size and found that the odds ratio was now 1.8. Assuming systematic errors were controlled for in study design, data collection and analysis, this difference can be explained by random error/sampling variation. A third sample might reveal an odds ratio of 1.1 or 2.5, which demonstrates that sampling variation is both unpredictable and not reproducible. In general, epidemiologists try to reduce sampling variation by increasing sample size. The stronger the relationship between the exposure and outcome, the smaller the group of patients that need to be studied for this relationship to be apparent. If the group being studied is too small, then the causal relationship may be missed, or spurious results may show up by sampling variation and random error.

## **V. STUDY DESIGN CONSIDERATIONS**

The purpose of epidemiology is to establish associations between exposures and outcomes that may uncover clues to causation. Epidemiologists can explore the relationship between exposure and outcome in humans in real-world situations by observing (observational study designs) or intervening to a limited extent (experimental study designs), as opposed to controlling all aspects of an experiment in the laboratory. Epidemiologists may also gather data from many studies, either observational or experimental (meta-analysis study designs) and summarize the information in an attempt to demonstrate associations between exposure and outcome. As such, there are many different study designs in epidemiologic research in humans, each with strengths and weaknesses.

### ***A. Case Reports And Case Series***

Individual level observations can be documented in a case report, a particular clinical situation involving one unique patient, or in a case series, a description of a group of patients with similar clinical findings or conditions. Case reports and case series are helpful tools in generating hypotheses about associations between exposures and outcomes. However, the lack of a comparison group and the likely presence of bias and confounding limit validity, and therefore limit the ability of these types of epidemiologic descriptions to establish causal associations between exposure and outcome.

### ***B. Cross-Sectional Studies***

A common epidemiologic study design used in the initial attempts to evaluate associations between exposures and outcomes is the cross-sectional study. In this type of study, both the exposure and outcome are evaluated simultaneously in each study participant. This approach is sometimes referred to as a prevalence study, as cases of disease or outcome identified are prevalent cases of the outcome being investigated. It is impossible to determine the temporality between exposure and outcome with this epidemiologic study design because of the temporal bias that may exist if the disease causes the exposure. For instance, prevalent cases of asthma may be less likely to own a cat than those without asthma. As patients with asthma may have been instructed to not own a cat,

this relationship might lead investigators to conclude that cat ownership is protective against asthma, leading to a phenomenon known as reverse causality. In addition to temporal bias, selection bias due to survivorship may also be present in cross-sectional studies. This may result if exposure in cases leads to shortened survival than those cases who are unexposed. Similar to case-reports and case-series, cross-sectional studies are often used to generate hypotheses about potential causal associations between exposure and outcome.

### ***C. Case-Control Studies***

Another common study design used to evaluate the effect of an exposure on an outcome is known as a case-control study. In this type of epidemiologic study, cases are defined as those with a particular outcome and non-cases or controls are defined as those without a certain outcome. Exposure is then retrospectively evaluated and compared between the cases and controls. Thus, in a case-control study, the prevalence of the exposure of interest should be higher among those with the outcome (cases) than those without the outcome (controls). In general, case-control studies provide more information on the temporal relationship between exposure and outcome than cross-sectional studies. However, case-control studies remain susceptible to other forms of bias. Selection bias can occur in a case-control study when the relationship between exposure and outcome differs systematically between the study population and the source population. Because of this, selection bias can sometimes lead to an association when one does not actually exist. Recall bias is common in case-control studies and results from the cases or subjects with disease having a tendency to remember past exposures more than controls. As mentioned above, it may also arise if cases are more likely to investigate possible factors that may increase the risk of developing a certain disease. Recall bias is often less likely to occur when both cases and controls are patients, for example, in hospitalized patients<sup>14</sup> as compared to population-based case-control studies where the degree of thinking about a possible exposure or outcome is likely to be at similar levels.

### ***D. Cohort Studies***

A cohort design assigns an individual as either exposed or unexposed and then that individual is followed over time to see if a particular outcome of interest develops. In general, there are two main types of cohort studies – prospective and retrospective. A prospective cohort design establishes exposure status in the beginning of a study and potentially repeatedly during the study, and then the outcome status for each individual is determined during a follow-up period that extends into the future. In a retrospective cohort design, the exposure and outcome have already occurred (as in the use of administrative or registry data), and the exposure status of each individual is determined from a time period that existed in the past with the outcome then being determined during a time period after exposure that may extend to the present. Temporality is established whether a cohort study is prospective or retrospective in design because the exposure status is always determined prior to evaluating outcome status. In general, cohort studies provide more evidence for a causal relationship between exposure and outcome, and can often study many exposure-outcome relationships with less chance for bias and confounding than case-control studies if

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<sup>14</sup> Oleckno (2008) at 207; Infante-Rivard, *Hospital or Population Controls for Case-Control Studies of Severe Childhood Diseases?* (2003) 157(2) *Am J Epidemiol* 176.

the design, conduct, data collection and analysis are properly performed. However, cohort study designs also remain susceptible to certain types of bias and confounding, are often very expensive, take a long time to conduct and may be difficult to perform, especially if the outcome of interest is rare.

### ***E. Experimental Studies***

Unlike an observational study, where exposure is not under the control of the investigator, an experimental study is one in which the exposure (intervention) is controlled directly by the investigator. One such experimental study design – the randomized-controlled clinical trial – is a planned epidemiologic experiment where subjects are randomly assigned to an exposure (intervention) or control group to evaluate the effect of the exposure on outcome. Randomized controlled clinical trials are considered the gold standard of epidemiologic studies. Although there are many advantages to an experimental study design, experimental studies are still subject to the effects of bias and confounding if not designed and conducted properly, and there are instances when this design is not suitable to evaluate the causal association between exposure and outcome because of potential for harm, lack of equipoise or ethical concerns.

### ***F. Meta-Analysis***

Epidemiologists may use multiple studies that address the same research question to provide an overall statistical summary of the results. This process is known as meta-analysis and is useful when individual studies tend to be inconclusive because of small sample size. A meta-analysis can provide a precise estimate of the effect of an exposure on an outcome of interest by combining the results of relevant studies by using a systematic approach and analysis. Meta-analyses can also help to provide consensus about the effectiveness of interventions, as well as insight or explanation for differences in individual trial results. Meta-analysis is a type of systematic review that utilizes a comprehensive, rigorous and standardized approach to selecting, assessing and synthesizing all relevant studies on a given topic. Systematic reviews that summarize studies without combining the results statistically are often called qualitative systematic reviews, while those that also combine study results statistically to produce an overall summary effect are referred to as quantitative systematic reviews, and are synonymous with meta-analyses. There are fundamental steps that must be followed to ensure the quality of a meta-analysis. These include (a) defining the research question, (b) defining the criteria for study selection, (c) structuring a review of the literature for all eligible studies, (d) structuring data abstraction, (e) reviewing the methods and results of each study critically, (f) summarizing the results of each study using a standard format, (g) using proper statistical tests to provide a summary effect, (h) assessing variation (heterogeneity) between studies and (i) reviewing, interpreting and reporting the findings.<sup>15</sup>

The idea of a meta-analysis is to combine the results of individual studies so that a summary point estimate can be reached that describes the strength of association between exposure and outcome. There are different approaches to modelling data between studies, and it is important to understand that these approaches may produce different results. Fixed-effects models assume that the effect of exposure on outcome is equal in all studies

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<sup>15</sup> Oleckno (2008).

included in the meta-analysis, while random-effects models assume that the effect of exposure on outcome varies between each included study due to both actual differences in effect and random error. In general, when the findings of the included studies are similar, both models yield similar summary estimates, but when the findings of the included studies vary appreciably, the models may produce conflicting results. A statistical test of heterogeneity is oftentimes performed to evaluate whether differing results from the included studies are due to chance alone. If unlikely due to chance, then a random effects model may be more appropriate.

It is also important to understand that in addition to the great deal of preparation and structured organization that is involved in conducting a meta-analysis, it is of utmost importance to vigilantly examine the accuracy of the included individual studies when relying on meta-analyses. Many of plaintiffs' epidemiologists, for instance, premise their causation opinions in large part on the various meta-analyses assessing the effect of exposure to talc on ovarian cancer.<sup>16</sup> But, when it comes to concerns over bias and confounding, a pooled analysis or a meta-analysis will only be as good as the included studies. And while some of plaintiffs' experts have performed their own meta-analyses, the underlying limitations of the included studies are not lessened or removed simply by performing additional meta-analyses using the same studies with different groupings.

## **VI. EPIDEMIOLOGIC STUDIES OF TALC POWDER AND OVARIAN CANCER**

In order to understand the relationship between talc exposure and ovarian cancer, I have performed a search of the peer-reviewed literature. I identified 44 individual studies investigating the exposure/outcome relationship between talcum powder use and ovarian cancer. The individual studies were evaluated with attention to study design, accuracy, exposure assessment, analysis and validity, while noting both strengths and weaknesses.

### ***A. Summary Of Article Study Designs***

Due to the exposure (talc powder) and outcome (ovarian cancer) being studied, there were no experimental studies, as this study design would not be suitable to evaluate this relationship. The studies identified can be separated into three categories: (1) case-control studies, (2) cohort studies, and (3) meta-analyses. I reviewed 33 case-control studies (two of which pooled data from different studies), four cohort studies, and seven meta-analyses published between 1982 and 2018.<sup>17</sup>

The 33 case-control studies ranged in size from 123 to 4,092 participants. There were seven hospital-based case-control studies and 26 population-based case-control studies that I reviewed. The assessment of exposure varied extensively in the case-control studies and was obtained from responses to questionnaires on the use of talc, diaphragm with talc, diaphragm storage only, all over body talc, genital talc, legs only talc, not genital talc, talcum powder in the perineum, talcum powder on sanitary pads, talcum powder on

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<sup>16</sup> Clarke-Pearson Rep. 7; McTiernan Report 8, 63; Moorman Rep. 10.

<sup>17</sup> I also briefly reviewed the unpublished Taher meta-analysis cited by several of plaintiffs' experts, and it does not affect my analysis. The association it reports is not materially higher than prior studies, and it agrees with IARC's assessment that a causal relationship is merely "possible" in light of current evidence.

diaphragms, after bathing only, baby powder only, deodorizing powder, dusting powder to the perineum, any dusting powder, talc around the abdomen/ perineum, perineal dusting, genital powder application, genital/rectal talc, powder to genitals, powder to diaphragm, or powder to sanitary napkins. All studies included pathologically confirmed cases or cancer registry cases of ovarian cancer. Analyses varied widely among the case-control studies from no adjustment for potential confounders to adjusting for varying degrees of confounding, including age at first birth, age at last birth, age at menarche, age at menopause, tumor behavior, breast feeding, community-based case-control study, diaphragm use, duration of use, exercise, education, frequency of use, family history of breast and ovarian cancer, histologic type, hospital-based case-control study, hair dye use, hormone replacement therapy, hysterectomy, income, use of medications, menopausal status, sanitary napkin use, number of pregnancies, oral contraceptive use, parity, socioeconomic status, timing of use and tubal ligation.

The four cohort studies I reviewed utilized data from the US Nurses' Health Study (NHS), US Nurses' Health Study II, the Women's Health Initiative Observational Study, and the Sister Study and ranged in size from 41,654 to 108,870 participants. The assessment of exposure was obtained from responses to questionnaires on talc use, talc on the perineum or napkin, powder on the genitals, powder on diaphragm, powder on napkin or talc use in the past 12 months. Analyses varied across the different cohort studies with varying degrees of adjustment for potential confounding, including age, age at last birth, menopause status, age at menopause, race, parity, BMI, activity level, breast feeding, oral contraceptive use, duration of oral contraceptive use, estrogen use, postmenopausal hormone use, duration of hormone replacement therapy, tubal ligation, smoking status and family history of breast or ovarian cancer.

### ***B. Case-Control Studies: Hospital-Based***

I identified seven hospital-based case-control studies that have evaluated the potential causative association between talc and ovarian cancer, yielding similar non-statistically significant estimates of risk of ovarian cancer and talc usage.

In 1983, Hartge et al.<sup>18</sup> conducted a hospital-based case-control study of pathologically identified ovarian cancer and frequency matched controls of women in the same hospitals in Washington, DC. Interviews were performed and exposures were categorized as "any" use of talc and "genital" exposure to talc. Among women exposed to "any" talc, the odds ratio of ovarian cancer was not statistically significant at 0.7 (95% CI: 0.4-1.1). Among those who reported talc use on genitals, sanitary napkin or underwear, the odds ratio was not statistically significant at 2.5 (95% CI: 0.7-10.0). The study is limited by small sample size and lack of adjustment for potential confounders.

In 1988, Whittemore et al.<sup>19</sup> similarly completed a hospital-based case-control study of histologically confirmed ovarian cancer cases in pre-menopausal and postmenopausal women between the ages of 18 and 74 with primary epithelial ovarian cancer in Santa Clara County hospitals or at the University of California, San Francisco Medical Center and

<sup>18</sup> Hartge et al., *Talc and Ovarian Cancer*, (1983) 250 J. Am. Med. Ass'n 1844.

<sup>19</sup> Whittemore et. al., *Personal And Environmental Characteristics Related To Epithelial Ovarian Cancer*, (1988) 128 Am J. Epidemiol 1228.

hospitalized controls. In-person interviews were performed, and to evaluate exposure, subjects were asked about whether they had used talcum powder products on the perineum, sanitary pads and/or diaphragms. Participants who responded were asked about frequency and duration of use. Among women who reported perineum only talc use, the odds ratio was not statistically significant at 1.45 (95% CI: 0.81-2.60) after adjustment for parity and oral contraceptive use. There was no trend in increasing duration of treatment, and the risk of ovarian cancer was not statistically significant with increasing frequency of use.

Booth et al.<sup>20</sup> in 1989 performed a hospital-based case-control study of pathologically identified ovarian cancer in women under 65 years of age from 13 hospitals in London and two in Oxford and hospitalized controls. Subjects were interviewed and exposure was obtained through a questionnaire and frequency of talc use was reported as never, rarely, monthly, weekly or daily talc use. There was no statistically significant increase in risk of ovarian cancer between never and daily reported talc use (OR: 1.3; 95% CI: 0.8-1.9) after adjusting for age and social class. There was no trend of increased risk of ovarian cancer with increased frequency of reported talc use, as those participants who reported weekly use had a higher risk estimate (OR: 2.0; 95% CI: 1.3-3.4) than those who reported daily talc use, and no dose-response relationship with frequency of reported talc use was found among those exposed compared to those unexposed after adjusting for age and social class.

Rosenblatt et al.<sup>21</sup> in 1992 reported a hospital-based case-control study evaluating “fiber exposure” generally (with “fiber” defined as asbestos, talc or fiberglass), including “genital fiber use” specifically, which included an assessment of “method of application” in pathologically confirmed cases of ovarian cancer and hospitalized controls between 1981 and 1985 at the Johns Hopkins Hospital. A questionnaire was administered to participants, both by telephone and in the hospital, which was used to obtain reported exposure to talc and presence and length of applying talcum powder to the genital area. There was no statistically significant increase in risk of ovarian cancer with “genital fiber use” (OR: 1.0; 95% CI: 0.2-4.0) after adjustment for parity, or for exposures from diaphragm use with powder (OR: 3.0; 95% CI: 0.8-10.8) after adjustment for parity and education, or genital bath talc exposure (OR: 1.7; 95% CI: 0.7-3.9) in unadjusted analysis. There was also no statistically significant increase in the risk of ovarian cancer with length of exposure ( $\geq 37.4$  years vs.  $< 37.4$  years) to “genital fiber use” (OR: 2.4; 95% CI: 1.0-5.8) after adjustment for religion.

Tzonou et al.<sup>22</sup> in 1993 conducted a case-control study among hospitalized patients from two hospitals in Athens, Greece with histologically confirmed ovarian cancer and hospital visitor controls. In-hospital questionnaires were administered and exposure was obtained as reported use of talc in the perineal region. Even though the prevalence of talc usage was low, there was no statistically significant association between reported exposure of talc to the perineum and risk of ovarian cancer (OR: 1.05; 95% CI: 0.28-3.98). The

<sup>20</sup> Booth et al., Risk factors for ovarian cancer: a case-control study. (1989) 60(4) *Br J Cancer*. 592.

<sup>21</sup> Rosenblatt et al., *Mineral Fiber Exposure and the Development of Ovarian Cancer*, (1992) 45 *Gynecologic Oncology* 20.

<sup>22</sup> Tzonou et al., *Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer*. (1993) 55(3) *Int J Cancer*. 408.

authors adjusted for age, years of schooling, weight before onset of the disease, age at menarche, menopausal status, age at menopause, parity, age at first birth, tobacco smoking, consumption of alcoholic beverages, consumption of coffee, hair dyeing and analgesics-tranquilizers/hypnotics.

Hartge and Stewart<sup>23</sup> in 1994 reported a case-control study of women diagnosed with pathologically confirmed ovarian cancer in the Washington, DC area between 1978 and 1981. This study analyzed occupational history in women who were diagnosed with ovarian cancer and hospital-based controls. Trained interviewers used a standardized questionnaire that included lifetime job history and exposure to talc on the job. An industrial hygienist conducted an industrial hygiene exposure assessment evaluating each job/industry combination for potential exposure to talc, as well as other potential exposures. The risk of ovarian cancer was not significantly increased for any exposure to talc, regardless of the duration of exposure: <5 years (OR: 0.5; 95% CI: 0.1-1.4), 5-9 years (OR: 0.3; 95% CI: 0.1-1.4), 10+ years (OR: 0.5; 95% CI: 0.2-1.5).

Wong et al.<sup>24</sup> in 1999 reported the results of a hospital-based case-control study in patients with ovarian cancer as determined by the Roswell Park Tumor Registry and hospital-based controls. Exposure was evaluated using a self-administered questionnaire regarding medical history and personal hygiene. There was no statistically significant increased risk of ovarian cancer among participants who ever used talc (OR: 1.13; 95% CI: 0.88-1.44)<sup>25</sup> or among those who used talc on both a sanitary napkin and on the genital or thigh area (OR: 1.1; 95% CI: 0.7-1.7). There was a haphazard non-statistically-significant relationship with duration of talc use over time and risk of ovarian cancer: 1-9 years (OR: 0.9; 95% CI: 0.6-1.5), 10-19 years (OR: 1.4; 95% CI: 0.9-2.2), and ≥20 years (OR: 0.9; 95% CI: 0.6-1.2) after adjustment for parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location and history of tubal ligation or hysterectomy.

### ***C. Case-Control Studies: Population-Based***

I identified 26 population-based case-control studies (two from pooled data) that assessed the potential causative association between talc and ovarian cancer, yielding conflicting results.

Cramer et al.<sup>26</sup> in 1982 reported the first epidemiologic case-control study of genital talc use and risk of ovarian cancer. Cases were women diagnosed with ovarian cancer in the Greater Boston area between 1978 and 1981 and identified through pathology logs or tumor boards and confirmed pathologically. Controls were identified through annual

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<sup>23</sup> Hartge & Stewart., *Occupation and ovarian cancer: a case-control study in the Washington, DC, metropolitan area, 1978-1981*. (1994) 36(8) J Occup Med. 924.

<sup>24</sup> Wong et al. *Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study*. (1999) 93 Obstet Gynecol 372.

<sup>25</sup> The Wong paper does not report an odds ratio for ever versus never talc use, but the text of the article contains the information necessary to calculate it. Specifically, the text reports that 221 cases out of 421 total had ever used talc and 311 controls out of 693 total had ever used talc. The calculated odds ratio is 1.13 with a 95% CI of 0.88-1.44 (STATA SE 15.1, StataCorp, College Station, TX).

<sup>26</sup> Cramer et al., *Ovarian cancer and talc: a case-control study*. (1982) 50(2) Cancer 372.

listings of Massachusetts residents and were matched by residence, race and age. Subjects were interviewed in person to evaluate potential exposure to talc through contraceptives, hygiene or surgery. After adjustment for parity and menopausal status, a statistically significant association was found between “any perineal exposure” of talc and risk of ovarian cancer (OR: 1.92; 95% CI: 1.27-2.89).

Harlow and Weiss<sup>27</sup> in 1989 conducted a study of perineal use of powder and the risk of borderline ovarian cancer. Caucasian women aged 20-79 from three counties in Washington State diagnosed as having serous or mucinous borderline ovarian tumor were identified using the Seattle-Puget Sound Cancer Surveillance System during the years 1980 to 1985. Independent pathologic review was performed on 73% of cases. A control group was identified through random digit dialing. Reproductive, sexual and medical history, as well as information on talc exposure, was obtained during an in-person interview. There was no statistically significant increase in risk of borderline ovarian tumors with any perineal exposure to powder (OR: 1.1; 95% CI: 0.7-2.1), baby powder use (OR: 0.8; 95% CI: 0.4-1.9), or unspecified talc use (OR: 1.0; 95% CI: 0.4-2.4) after adjusting for age, parity and use of oral contraceptives. Use of deodorizing powder alone (OR: 3.5; 95% CI: 1.2-28.7) and use of deodorant powder alone or in combined use with another powder (OR: 2.8; 95% CI: 1.1-11.7) were both associated with a statistically significant increase in risk of borderline ovarian tumors after adjusting for age, parity and use of oral contraceptives.

Harlow et al.<sup>28</sup> in 1992 reported a case-control study among women 18 to 76 years of age diagnosed with borderline or malignant epithelial ovarian cancer confirmed pathologically from 10 hospitals in the Boston metropolitan area. Controls were selected from the Massachusetts Town Books. An in-person interview was performed to obtain demographic, occupational and medical history, as well as hygienic practices. Exposure was reported as any genital talc, type of application (sanitary napkin, underwear, partner or application to diaphragm, or dusting powder to the perineum) and brand of application (brand or generic baby powder or deodorizing or other scented powders). Application via dusting to the perineum was associated with a statistically significant risk of ovarian cancer (OR: 1.7; 95% CI: 1.1-2.7) after adjusting for parity, education, marital status, religion, use of sanitary napkins, douching, age and weight. Use of any genital talc was not associated with a statically significant increase in risk of ovarian cancer (OR: 1.5; 95% CI: 1.0-2.1) after adjusting for the same potential confounders. Although there was no statistically significant increase in risk of ovarian cancer with increasing lifetime total applications of talc-containing powders after adjusting for the same potential confounders, there was a statistically significant increase in the risk of ovarian cancer with more than 10,000 total lifetime perineal applications of talc-containing powders in participants with hysterectomy, tubal ligation and use during nonovulatory months (OR: 2.8; 95% CI: 1.4-5.4).

Chen et al.<sup>29</sup> in 1992 conducted a case-control study in China in women with pathologically confirmed cases of epithelial ovarian cancer. Controls were identified from

<sup>27</sup> Harlow & Weiss, *A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc*. (1989) 130(2) Am J Epidemiol. 390.

<sup>28</sup> Harlow et al., *Perineal exposure to talc and ovarian cancer risk*. (1992) 80(1) Obstet Gynecol. 19.

<sup>29</sup> Chen et al., *Risk factors for epithelial ovarian cancer in Beijing, China*. (1992) 21(1) Int J Epidemiol. 23.

the community using a random selection from a neighborhood committee or village. A questionnaire was developed and administered through face-to-face interviews by trained interviewers. There was no statistically significant association with using dusting powder to the lower abdomen and perineum and risk of ovarian cancer (OR: 3.9; 95% CI: 0.9-10.6) after adjusting for education and parity.

Cramer and Xu<sup>30</sup> in 1995 reported on a case-control study of women in the Greater Boston area diagnosed with ovarian cancer. The study combined women diagnosed with ovarian cancer from area hospitals between 1984 and 1987 and confirmed pathologically with a previous study of women diagnosed between 1978 and 1981. Controls were selected from the general population and matched by age and residence. In an unadjusted analysis, talc use was associated with an increase in risk of ovarian cancer (OR: 1.6; 95% CI: 1.2-2.1).

In 1995, Purdie et al.<sup>31</sup> conducted a case-control study in three Australian states of women diagnosed with ovarian cancer that was confirmed pathologically. Controls were drawn at random from the electoral roll and stratified by age and geographic region. Trained interviewers administered a questionnaire in a face-to-face interview, which included questions about marital status, education, ethnicity, height, weight, smoking history, occupation, medical history and history of talc use. Talc use around the abdomen/perineum was associated with an increased risk of ovarian cancer (OR 1.27; 95% CI: 1.04-1.54) after adjusting for parity.

Green et al.<sup>32</sup> in 1997 performed a case-control study using the study population from the Purdie study. Methods for case and control identification were similar to the Purdie study. Ever douching was associated with a non-significant 60% increase in risk of ovarian cancer. Use of talc in the perineal region was associated with an increased risk of ovarian cancer (OR: 1.3; 95% CI: 1.1-1.6) after adjustment for parity, oral contraceptive use, age, education, body mass index, smoking and family history of ovarian cancer. Even though there was a reported 60% increase in risk of ovarian cancer for those who ever-douched, there were no adjustments in multivariable analyses for douching as a potential confounder.

Shushan et al.<sup>33</sup> in 1996 conducted a case-control study of women aged 36 to 64 years with histologically diagnosed primary invasive or borderline epithelial ovarian cancer. Cases were identified through the Israel Cancer Registry. Controls were identified by telephoning randomly selected numbers within the same area codes as the cases. Cases and controls were interviewed using a questionnaire containing details on medical history and exposures. Exposure to talc was recorded as never-seldom and moderate-a lot talc use. A

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<sup>30</sup> Cramer & Xu, *Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer*. (1995) 5 Ann Epidemiol. 310.

<sup>31</sup> Purdie et al., *Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study*. Survey of Women's Health Study Group. (1995) 62(6) Int J Cancer. 678.

<sup>32</sup> Green et al., *Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer*. Survey of Women's Health Study Group. (1997) 71(6) Int J Cancer. 948.

<sup>33</sup> Shushan et al., *Human menopausal gonadotropin and the risk of epithelial ovarian cancer\**. (1996) 65(1) Fertil Steril. 13.

larger proportion of cases reported moderate-a lot of talc use when compared with controls (10.5% vs. 5.6%;  $p=0.04$ ) without adjusting for potential confounders.

Chang and Risch<sup>34</sup> in 1997 reported a case-control study among women diagnosed with histologically confirmed borderline and invasive ovarian cancers in Toronto and southern Ontario. Controls were identified through the Ontario Ministry of Finance and random selection based on geographic residence. A questionnaire was developed and administered in-person, in-home. Exposure to talc was evaluated by reported regular talc use, use of talc/cornstarch combination, talc use with a sanitary napkin, talc use after bathing as well as after bath uses per month, and years of after bath use. Although there was a significant increase in risk of ovarian cancer with any talc exposure (OR: 1.42; 95% CI: 1.08-1.86), there was no dose-response, and in fact there was a non-statistically significant inverse trend for after bath uses per month: <10 (OR: 1.84; 95% CI: 1.24-2.73), 10-25 (OR: 1.13; 95% CI: 0.74-1.72), >25 (OR: 0.95; 95% CI: 0.61-1.49) and for years of after bath use: <30 (OR: 1.7; 95% CI: 1.09-2.64), 30-40 (OR: 1.44; 95% CI: 0.96-2.15), >40 (OR: 0.87; 95% CI: 0.54-1.38) after adjusting for age at time of interview, years of oral contraceptive use, number of full-term pregnancies, average duration of breastfeeding per pregnancy, the occurrence of a tubal ligation or hysterectomy, and having a mother/sister with ovarian or breast carcinoma.

Cook et al.<sup>35</sup> in 1997 conducted a case-control study of women diagnosed with invasive or borderline epithelial ovarian cancer from records of the Cancer Surveillance System of western Washington State from 1986 through 1988. Controls were identified by random digit dialing of a larger control pool for other studies of cancer in women. Information regarding genital powder exposure was collected by in-person interviews. The occurrence of lifetime genital powder application and the exclusive use of types of genital powder application, including perineal dusting, diaphragm storage in powder, powder on sanitary napkins and genital deodorant spray, were collected. Reported exposure also included cumulative lifetime days of use for perineal dusting, cumulative lifetime months for diaphragm storage in powder, cumulative lifetime months for powder on sanitary napkins and cumulative lifetime months for genital deodorant spray. The use of different types of powder, including talcum powder, baby powder, cornstarch, deodorizing powder, bath or body powder and unspecified powder, was also reported. Although there was an increase in risk of ovarian cancer in women who dusted their perineal areas with powder after bathing (OR: 1.8; 95% CI: 1.2-2.9), there was no statically significant increase in risk of ovarian cancer with increasing cumulative lifetime days of any perineal dusting. There was also no statistically significant increase in risk of ovarian cancer with exclusive use of talcum powder (OR: 1.2; 95% CI: 0.6-2.5) or with the use of any talcum powder (OR: 1.6; 95% CI: 0.9-2.8) after adjusting for age.

Godard et al.<sup>36</sup> in 1998 reported a case-control study of women with histologic diagnosis of ovarian cancer through the gynecologic oncology clinics of two large teaching

<sup>34</sup> Chang & Risch, *Perineal talc exposure and risk of ovarian carcinoma*. (1997) 79(12) Cancer. 2396.

<sup>35</sup> Cook et al., *Perineal powder exposure and the risk of ovarian cancer*. (1997) 145(5) Am J Epidemiol. 459.

<sup>36</sup> Godard et al., *Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study*. (1998) 179(2) Am J Obstet Gynecol. 403.

hospitals in Montreal in 1995 and 1996. Controls were obtained through random digit dialing. A questionnaire was developed and administered either in-person or on the phone to obtain medical history and reported exposure to talc on perineum. Talc on the perineum was not statistically associated with an increase in ovarian cancer (OR: 2.49; 95% CI: 0.94-6.58) after adjusting for age at diagnosis, age at last childbirth, age at menarche, age at last oral contraceptive use, tubal ligation or hysterectomy and alcohol use.

Cramer et al.<sup>37</sup> in 1999 conducted a case-control study of women with newly diagnosed ovarian cancer in eastern Massachusetts or New Hampshire identified through tumor boards and statewide cancer registries with review of pathology reports. Controls were identified through random digit dialing. Participants were interviewed in-person using a standardized questionnaire and asked if they regularly used talc, baby powder, or deodorant powder dusted or sprayed on “feet, arms, or other non-genital areas, to the genital or rectal area, on sanitary napkins, or on underwear” as well as a husband’s use of powder in his genital area. “[T]ypes of powder(s) used, applications per month and total years of use were assessed in talc users.” Any reported personal genital exposure was associated with increased risk of ovarian cancer (1.60; 95% CI: 1.18-2.15) after adjusting for age, study center, tubal ligation, BMI, parity, oral contraceptive use, or primary relative with breast or ovarian cancer. Risk of ovarian cancer increased and then fell (inverse relationship) with increasing years of talc use and with increasing total applications, although these estimates were not statistically significant.

Ness et al.<sup>38</sup> in 2000 reported a case-control study of women diagnosed with ovarian cancer who were identified from 39 hospitals in the Delaware Valley region. Controls were identified through random digit dialing. Statistically significant associations were observed for the use of talc on the feet, etc. (OR: 1.4; 95% CI: 1.1-1.6), the genital/rectal area (OR: 1.5; 95% CI: 1.1-2.0), sanitary napkins (OR: 1.6; 95% CI: 1.1-2.3) and underwear (OR: 1.7; 95% CI: 1.2-2.4) after adjusting for age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy and breast-feeding. Risk of ovarian cancer increased and then fell (inverse relationship) with increasing years of talc use and with increasing total applications, although these estimates were not statistically significant.

Mills et al.<sup>39</sup> in 2004 reported a case-control study of epithelial ovarian cancer in 22 counties of Central California and identified cases through two regional cancer registries as women diagnosed with pathologically confirmed epithelial ovarian cancer from 2000 through 2001. Controls were women 18 years or older selected by random digit dialing. All cases and controls were interviewed by telephone to obtain information on history of adult use of talcum powder in the genital area, calendar year(s) of use, frequency of use, and total duration of use. Although there was a statistically significant increase in risk of ovarian cancer with ever talc use (OR: 1.37; 95% CI: 1.02-1.85) after adjusting for age, race/ethnicity, duration of oral contraceptive use and breast feeding, there was no clear

<sup>37</sup> Cramer et al., *Genital talc exposure and risk of ovarian cancer*. (1999) 81(3) Int J Cancer. 351.

<sup>38</sup> Ness et al., *Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer*. (2000) 11(2) Epidemiology 111.

<sup>39</sup> Mills et al., *Perineal Talc Exposure and Epithelial Ovarian Cancer Risk in the Central Valley of California*. (2004) 112 Int’l J. Cancer 458.

dose-response with relation to frequency and duration of talc use and risk of ovarian cancer after adjusting for the same potential confounders. There was a haphazard relationship between reported frequency of use and risk of ovarian cancer, with estimates increasing with rare to several time a month use, then decreasing with 1-3 times per week, and finally increasing with 4-7 times per week. Similarly, there was a haphazard relationship between duration of use and risk of ovarian cancer, as estimates increased at 4-12 years, then decreased at 13-30 years and decreased further at >30 years reported exposure.

Pike et al.<sup>40</sup> in 2004 conducted a case-control study of women in Los Angeles County with histologically confirmed ovarian cancer or borderline tumors identified by the Cancer Surveillance Program between 18 and 74 years of age from 1992 to 1998. Controls were identified using a systematic algorithm based on the address of the patient. Participants were interviewed in person using a questionnaire covering medical and personal lifestyle history. Genital area talc usage was associated with a statistically significant increase in risk of ovarian cancer (OR: 1.60; 95% CI: 1.18-2.18) after adjustment for ethnicity, age, education, family history of ovarian cancer, tubal ligation, BMI, parity, age at last childbirth, number of births, number of incomplete pregnancies, oral contraceptive use, menopausal status, age at menopause and estrogen-progesterone therapy.

Jordan et al.<sup>41</sup> in 2007 reported a case-control study of women aged 18-79 years with histologically confirmed invasive and borderline ovarian cancer in Australia identified by the Australian Ovarian Cancer Study and state-based cancer registries between 2002 and 2005. Women with benign mucinous tumors were also identified by the Australian Ovarian Cancer Study and through records from three major pathology laboratories. Controls were randomly selected from the Australian Electoral Roll after stratifying for age and state. Participants were asked to complete and return a health and lifestyle questionnaire. Neither moderate talc use in the perineal region (OR: 0.4; 95% CI: 0.1-2.0) nor substantial talc use in the perineal region (OR: 1.0; 95% CI: 0.4-2.1) was associated with a statistically significant increase in risk of invasive mucinous ovarian cancer after adjustment for age, education level, parity, use of oral contraceptives, hysterectomy, tubal ligation and smoking status.

Gates et al.<sup>42</sup> in 2008 reported a nested case-control study of talc use, variants in the GSTM1, GSTT1 and NAT2 genes, and the risk of ovarian cancer using cases from the New England Case-Control Study (NECC) and the Nurses' Health Study (NHS). The "NECC questionnaires included multiple questions about regular use of talcum, baby or deodorizing powder as an adult. Specific questions were asked about type of use (as a dusting powder to the genital area, sanitary napkins, underwear or non-genital areas), frequency of use, age at first use, number of years used and brand of powder used. The 1982 NHS questionnaire requested information on whether the participant had ever commonly applied talcum, baby

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<sup>40</sup> Pike et al., *Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study*. (2004) 82(1) Fertil Steril. 186.

<sup>41</sup> Jordan SJ, Green AC, Whiteman DC, Webb PM, Australian Ovarian Cancer Study Group. *Risk factors for benign, borderline and invasive mucinous ovarian tumors: epidemiological evidence of a neoplastic continuum?* (2007) 107(2) Gynecol Oncol 223.

<sup>42</sup> Gates et al., *Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer*. (2008) 17(9) Cancer Epidemiol Biomarkers 2436.

or deodorizing powder to the perineal area (no, <once/week, 1-6 times/week or daily) or to sanitary napkins (yes/no).” There was a statistically significant increase in the risk of ovarian cancer with regular genital talc use in participants from the NECC study (OR: 1.62; 95% CI: 1.26-2.09) but no statistically significant increase in risk of ovarian cancer with regular talc use in the NHS (OR: 1.48; 95% CI: 0.82-2.68). Similarly, there was a statistically significant increase in the risk of ovarian cancer with daily genital talc use in participants from the NECC study (OR: 1.61; 95% CI: 1.18-2.2) but no statistically significant increase in risk of ovarian cancer with regular talc use in the NHS (OR: 1.34; 95% CI: 0.65-2.76). Regular genital talc use was associated with a statistically significant increase in risk of ovarian cancer using the combined study population (OR: 1.36; 95% CI: 1.14-1.63) after adjustment for duration of oral contraceptive use, parity, tubal ligation, BMI and duration of hormone replacement therapy. There was no clear dose-response with regard to frequency of genital talc use, with estimates falling with less than once a week usage and then rising with 1-6 times a week and daily usage.

Merritt et al.<sup>43</sup> in 2008 reported the Australian Ovarian Cancer Study, which was an Australia-wide case-control study of epithelial ovarian cancer. Cases were women diagnosed with invasive or low malignant potential ovarian cancer aged 18 to 79 years between 2002 and 2005. Controls were selected from the Australia Electoral Roll. Study participants filled out a comprehensive health and lifestyle questionnaire. “To determine use of talcum powder in the perineal region, participants were asked whether they had ever used powder or talc in the genital area or on underwear or sanitary pads/diaphragm. They were asked their age at first use and years of talc use in these areas.” Ever perineal use of talcum powder was associated with a statistically significant increase in risk of ovarian cancer (OR: 1.17; 95% CI: 1.01-1.36) after adjusting for age, education, parity and oral contraceptive use. However, there was no clear dose-response relationship, with a random shape of the exposure-response curve between perineal use of talcum powder and risk of ovarian cancer as well as the risk of cancer subtypes.

Moorman et al.<sup>44</sup> in 2009 reported a case-control study of epithelial ovarian cancer conducted in a 48-county region of North Carolina between 1999 and 2008. Cases were identified through the North Carolina Cancer Registry and were confirmed histopathologically. Controls were obtained from the same geographic region through random digit dialing. In-person questionnaires were administered, which included questions on medical history and lifestyle factors, including talc ever use. There was no statistically significant increase in risk of ovarian cancer with ever talc use among both white women (OR: 1.04; 95% CI: 0.82-1.33) and African Americans (OR: 1.19; 95% CI: 0.68-2.09) after adjusting for age.

In 2009, Wu et al.<sup>45</sup> conducted a case-control study of residents of Los Angeles County between the ages of 18 and 74 who had histologically confirmed invasive or

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<sup>43</sup> Merritt et al., *Talcum Powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer*. (2008) 122 Int’l J. Cancer 170.

<sup>44</sup> Moorman et al., *Ovarian Cancer Risk Factors in African-American and White Women*. (2009) 170(5) Am J Epidemiol 598.

<sup>45</sup> Wu et al., *Markers of inflammation and risk of ovarian cancer in Los Angeles County*. (2009) 124 Int’l J. Cancer 1409.

borderline ovarian cancer diagnosed from 1998 through 2002. Cases were identified by the Cancer Surveillance Program. Controls were identified using a neighborhood recruitment algorithm. Participants were interviewed using a questionnaire that covered medical, gynecological, reproductive and lifestyle history. To determine use of talcum powder, subjects were asked if they ever used talc at least once per month for six months or more. If the response was positive, participants were asked if “they had ever used talc in nonperineal areas (feet, arms, chest or back), perineal areas, or on underwear or sanitary pads/diaphragm,” as well “frequency of use (times per month) and years of talc use.” Ever talc use was associated with a statistically significant risk of ovarian cancer (OR: 1.48; 95% CI: 1.15-1.91) as was talc applied to the perineal area (OR: 1.53; 95% CI: 1.13-2.09) after adjusting for race/ethnicity, age, education, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity. A statistically significant increase in risk of ovarian cancer was also seen in those who used talc for more than 20 years and more than 30 times per month (OR: 2.08; 95% CI: 1.34-3.23) and in those who had more than 52,000 talc uses (OR: 1.99; 95% CI: 1.34-2.96).

Rosenblatt et al.<sup>46</sup> in 2011 reported a case-control study of women from a 13-county area of Washington State who were 35 to 74 years old and who were diagnosed with invasive or borderline epithelial ovarian tumor between 2002 and 2005. Cases were identified through the Cancer Surveillance System and controls were selected by random digit dialing. In-person interviews were performed, and obtained information on demographic and lifestyle characteristics, medical history and obstetrical history. For powder use on sanitary napkins and deodorant spray, investigators recorded the total number of months of use. For the use of powder on the perineum after bathing, only intervals of at least one year when powder was usually used was recorded. Women were also asked to report the “types of powder(s) used after bathing, including talcum, baby, cornstarch, deodorant, body/bath, and other or unknown. The extent of exposure to perineal powder after bathing was assessed as lifetime duration of use . . . and as the estimated lifetime number of applications.” There was no statistically significant increase in the risk of ovarian cancer for using powder after bathing (OR: 1.27; 95% CI: 0.97-1.66) after adjusting for age, calendar year of diagnosis/reference date, county of residence, number of full-term births and duration of hormonal contraception.

Kurta et al.<sup>47</sup> in 2012 conducted a case-control study using data from the Hormones and Ovarian Cancer Prediction (HOPE) study. Cases were residents of Western Pennsylvania, Eastern Ohio and Western New York State and had histologically confirmed ovarian, peritoneal or fallopian tube cancers diagnosed between 2003 and 2008. Controls were frequency matched and identified through random digit dialing. Trained interviewers collected questionnaire data that included medical history and information about lifestyle. “Perineal talc use was defined as ever using dusting powder or deodorizing spray on the genital or rectal areas, on sanitary napkins, on underwear, or on diaphragms or cervical caps.” Perineal talc use was associated with a statistically significant increase in risk of ovarian cancer (OR: 1.40; 95% CI: 1.16-1.69) after adjusting for age and education.

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<sup>46</sup> Rosenblatt et al., *Genital powder exposure and the risk of epithelial ovarian cancer*. (2011) 22 Cancer Causes Control 737.

<sup>47</sup> Kurta et al., *Use of Fertility Drugs and Risk of Ovarian Cancer: Results from a U.S.-Based Case-Control Study*. (2012) 21(8) Cancer Epidemiol Biomarkers Prev. 1282.

Terry et al.<sup>48</sup> in 2013 reported on a pooled analysis of case-control studies using data from the Ovarian Cancer Association Consortium. Investigators used data from eight case-control studies and included 8,525 cases of ovarian, fallopian tube or peritoneal cancer and 9,859 controls. Genital powder use was defined as “any type of powder (talc, baby, deodorizing, cornstarch, or unspecified/unknown) applied directly or indirectly (by application to sanitary pads, tampons, or underwear) to the genital, perineal, or rectal area.” Criteria for regular use varied between studies from “ever use” to “one year or longer.” “Women who reported both genital and non-genital powder use were classified as genital users.” Genital use of powder was associated with a statistically significant increase in risk of ovarian cancer when compared with no powder use (OR: 1.24; 95% CI: 1.15-1.33) after adjusting for age, oral contraceptive use, parity, tubal ligation history, BMI and race/ethnicity.

Wu et al.<sup>49</sup> in 2015 reported a case-control study of women with newly diagnosed histologically confirmed invasive epithelial ovarian cancer identified through the Cancer Surveillance Program. Cases were non-Hispanic white, Hispanic, or African American women aged 18 to 74 diagnosed between 2003 and 2008. In-person interviews were conducted using questionnaires, which included questions on demographics, lifestyle, medical history, family history and genital talc use. Results are based on pooling of four case-control studies in Los Angeles County investigating invasive epithelial ovarian cancer. Genital talc use was associated with a statistically significant increase in risk for invasive ovarian cancer in all study participants (OR: 1.46; 95% CI: 1.27-1.69); non-Hispanic whites (OR: 1.41; 95% CI: 1.21-1.67) and Hispanics (OR: 1.77; 95% CI: 1.20-2.62), but not in African Americans (OR: 1.56; 95% CI: 0.80-3.04). Every five years of talc use was also associated with a statistically significant increase in risk for invasive ovarian cancer in non-Hispanic whites (OR: 1.14; 95% CI: 1.08-1.21) and Hispanics (OR: 1.18; 95% CI: 1.02-1.36), but not in African Americans (OR: 1.15; 95% CI: 0.90-1.47). Estimates were adjusted for menopausal status, age at menarche, hormone therapy use, BMI, income, education, parity, oral contraceptive use, tubal ligation, endometriosis and family history of ovarian cancer.

Schildkraut et al.<sup>50</sup> in 2016 reported a case-control study of women enrolled in the African American Cancer Epidemiology Study from 11 locations in the United States. Cases included African American women aged 20 to 79 with newly diagnosed ovarian cancer. Controls were African American women who were identified through random digit dialing. Participants completed a baseline telephone interview, which includes questions on demographics, medical history and information on lifestyle. “[P]articipants were asked whether they had ever regularly used talc, cornstarch, baby, or deodorizing powders. Participants were considered ‘regular users’ if they reported using any of these powders at least one time per month for at least six months, and ‘never users’ if they did not. Regular users were asked about their frequency and duration of use, age at first use, and whether

<sup>48</sup> Terry et al., *Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls*. (2013) 6(8) *Cancer Prev Res* 811.

<sup>49</sup> Wu et al., *African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates*. (2015) 24(7) *Cancer Epidemiol Biomarkers Prev*. 1094 (“Wu 2015”).

<sup>50</sup> Schildkraut (2016).

they applied powders to genital areas (including on underwear or sanitary napkins, or on birth control devices like diaphragms) and/or nongenital areas.” There was a statistically significant increase in the risk of ovarian cancer with any genital use of powder (OR: 1.44; 95% CI: 1.11-1.86) after adjusting for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of oral contraceptive use, first-degree family history of breast or ovarian cancer and interview year. In addition, as discussed above, when investigators stratified by the interview date, there was no statistically significant association between ovarian cancer and any genital use of body powder if the interview date was before 2014 (OR: 1.19; 95% CI: 0.87-1.63), but if the interview date was after 2014, there was a statistically significant increase in risk of ovarian cancer with any genital use of body powder (OR: 2.91; 95% CI: 1.70-4.97), after adjusting for the same potential confounders.

Cramer et al.<sup>51</sup> in 2016 reported a pooled analysis of case-control studies of women residing in Eastern Massachusetts and New Hampshire diagnosed with ovarian cancer between the ages of 18 and 80 using data from the NHS and several sites from the Ovarian Cancer Association Consortium. Controls were identified through random digit dialing. Participants “were asked whether they ‘regularly’ or ‘at least monthly’ applied powder to the genital or rectal area, sanitary napkins or tampons, underwear, or areas other than the genital-rectal area. Additional details included type of powder, age begun, years used, and applications per month. Lifetime exposure was estimated by multiplying frequency of application per month by months used.” This was divided by 360 to yield talc-years, which were divided into separate quartiles for dose-response analysis. Any genital powder use was associated with a statistically significant increase in the risk of ovarian cancer (OR: 1.33; 95% CI: 1.16-1.52) after adjusting for reference age, study center and study phase. There was no clear pattern suggesting a dose-response effect, with a random sine wave pattern with increasing risk, then decreasing risk, then increasing risk with total genital talc applications.

#### ***D. Cohort Studies***

Gertig et al.<sup>52</sup> reported the relationship between perineal talc use and ovarian cancer using participants from the NHS. This is a prospective study of 121,700 registered nurses in the United States who were ages 30-55 years at enrollment in 1976. Talc exposure was not evaluated when the study began, but questions regarding talc exposure were added in 1982. 78,630 women completed the questions regarding talc at baseline and formed the cohort for analysis and were followed for 14 years (1982-1996). There were 307 women who were subsequently diagnosed with ovarian cancer. After adjusting for confounders, no statistically significant association was found with ever talc use, with a relative risk for ovarian cancer of 1.09 (95% CI: 0.86-1.37) when compared to never talc use. Similarly, no statistically significant association was found with daily talc use, with a relative risk of 1.12 (95% CI: 0.82-1.55) when compared with never talc after adjusting for age, parity, duration of oral contraceptive use, BMI, tubal ligation, smoking status and postmenopausal hormone use. There was an increase in risk of invasive serous ovarian cancer, with a relative risk of

<sup>51</sup> Cramer et al., *The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States*. (2016) 27(3) *Epidemiology* 334.

<sup>52</sup> Gertig et al., *Prospective Study of Talc Use and Ovarian Cancer*. (2000) 92 *J. Nat. Cancer Inst.* 249.

1.40 (95% CI: 1.02-1.91) among ever talc users when compared to never talc users after adjusting for the same potential confounders.

Gates et al.<sup>53</sup> examined the association between ovarian cancer risk factors and ovarian cancer by histological subtype in the NHS and Nurses' Health Study II (NHSII). This prospective study included 221,866 women who completed baseline and biennial follow-up providing information on lifestyle factors and disease diagnoses. Follow-up was longer than the Gertig study and was 24 years in the NHS (1982-2006) and six years in the NHSII. There were 924 women who subsequently developed ovarian cancer and 721 cases with the histologies of interest (496 serous invasive, 139 endometrioid, 86 mucinous). Information on regular talc use was collected in 1982 and available for NHS participants only (108,870 women). No statistically significant increases in risk were found between talc used greater than once weekly with all epithelial (RR: 1.06; 95% CI: 0.89-1.28), serous invasive (RR: 1.06; 95% CI: 0.84-1.35), endometrioid (RR: 1.06; 95% CI: 0.66-1.69), or mucinous (RR: 1.5; 95% CI: 0.84-2.66) ovarian cancer when compared with less than once weekly talc use after adjusting for age, BMI, activity level, parity, breastfeeding, oral contraceptive use, tubal ligation, age at menopause, estrogen use, menopause status, smoking status and family history of breast or ovarian cancer.

Houghton et al.<sup>54</sup> assessed the perineal powder use and the risk of ovarian cancer prospectively in the Women's Health Initiative observational cohort, which enrolled postmenopausal women aged 50-79 from 40 clinical centers across the United States from 1993 to 1998 through 2012. Participants completed annual questionnaires to obtain information on risk factors and outcomes, including ovarian cancer. Perineal powder was assessed via self-report at baseline by asking participants if they had ever used powder on their private parts (genital areas). Those who answered yes were asked questions regarding duration of use. Participants were also asked about use with diaphragms and sanitary napkins or pads. There were 61,576 women who completed baseline questionnaires and followed for a mean 12.4 years. There were 429 women who subsequently developed ovarian cancer. No statistically significant increase in risk of ovarian cancer between ever powder use on genitals (HR: 1.12; 95% CI: 0.92-1.36) and never powder use on genitals was found after adjusting for age, race, duration of oral contraceptive use, duration of hormone replacement therapy, family history, age at last birth, BMI, smoking status, tubal ligation and parity. There was also no statistically significant increase in risk from duration of use between talc use greater than 10 years (RR: 0.98; 95% CI: 0.75-1.29) or greater than 20 years (RR: 1.10; 95% CI: 0.82-1.48) when compared with never talc use after adjusting for the same potential confounders. Similarly, no statistically significant increase in risk was found for all serous (RR: 1.16; 95% CI: 0.88-1.53), serous invasive (RR: 1.13; 95% CI: 0.84-1.51), mucinous (RR: 1.03; 95% CI: 0.47-2.27), or endometrioid (RR: 1.29; 95% CI: 0.64-2.61) ovarian cancer between ever talc use and never talc use after adjusting for the same potential confounders.

<sup>53</sup> Gates et al., *Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype*. (2010) 171 Am. J. Epidemiology 45.

<sup>54</sup> Houghton et al., *Perineal Powder Use and Risk of Ovarian Cancer*. (2014) 106(9) J Nat. Cancer Inst.

Gonzalez et al.<sup>55</sup> evaluated the effect of douching and talc use on the risk of ovarian cancer prospectively in the Sister Study, which enrolled women aged 35 to 74 who had never had breast cancer and who had a sister or half-sister diagnosed with breast cancer in the United States and Puerto Rico from 2003 to 2009 through 2014. Participants completed computer-assisted telephone interviews, which included questions about lifestyle factors and health conditions. Participants also completed a self-administered questionnaire about personal products used in the 12 months prior to enrollment, which included questions about frequency of douching as well as talc use, method of talc use, and frequency of talc use. There were 50,884 women who completed questionnaires and, after excluding participants who had bilateral oophorectomies or ovarian cancer before enrollment or who had no follow-up information, 41,654 women were followed for a median of 6.6 years. There was no statistically significant increased risk of ovarian cancer (HR: 0.73; 95% CI: 0.44-1.2) with ever talc use during the 12 months prior to the study when compared with never talc use after adjusting for race, BMI, parity, duration of oral contraceptive use, baseline menopausal status and tubal ligation. There was, however, a statistically significant increase in risk of ovarian cancer (HR: 1.9; 95% CI: 1.2-2.9) with douching/no talc use when compared with neither use as well as an increased risk of ovarian cancer with douching in the past 12 months (HR: 1.8; 95% CI: 1.2-2.8) when compared with never douching after adjustment for the same potential confounders. This study highlights the potential for douching to be a confounder in previous investigations, and all but one study failed to control for the potential confounding effect of douching and risk of ovarian cancer.

#### *E. Summary Of Observational Studies*

Evaluating the association between talc use and ovarian cancer in case-control studies poses several challenges that require attention. The assessment of exposure is difficult because it is solely based on self-report. Talc purchasing and use are not documented in the medical records or available in pharmacy records. As there is no reliable method of confirming talc usage, the accuracy and validity of these studies even under perfect circumstances can be dramatically affected by reporting bias. Additionally, the quantification of talc exposure is very difficult and may be impossible to verify accurately. Powders have varying amounts of talc and can be applied by various methods, leading to more or less exposure. There is no standardized dose/amount that is used, and there is no standard quantification method with verification that has been universally employed among the studies in the medical literature. Various studies collected information on the reported use of talc, diaphragm with talc, diaphragm storage only, all over body talc, genital talc, legs only talc, not genital talc, talcum powder in the perineum, talcum powder on sanitary pads, talcum powder on diaphragms, after bathing only, baby powder only, deodorizing powder, dusting powder to the perineum, any dusting powder, talc around the abdomen/perineum, perineal dusting, genital powder application, genital/rectal talc, powder to genitals, powder to diaphragm, or powder to sanitary napkins. As such, there are no case-control or cohort epidemiologic studies or meta-analyses that have investigated the effect of a standardized amount of talc usage or a standardized method of use to ensure consistency of the assessment of exposure. In addition, only a few epidemiologic studies have found any dose-response relationship between genital talc use and ovarian cancer.

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<sup>55</sup> Gonzalez (2016).

Furthermore, as in all case-control studies, recall bias is also of great concern. This arises from the phenomenon that cases are more likely than controls to think about and remember past exposures. Recall bias leads to differential misclassification of exposure and a falsely elevated estimate of risk between talc exposure and ovarian cancer. This is especially important if an exposure such as talc appeared in the news or was discussed in the public arena as having a possible causative association with ovarian cancer. There is evidence to suggest that hospital-based case-control studies are less likely to be subject to recall bias than population-based case-control studies because the degree to which study subjects think about possible past exposure is more similar (given that both cases and controls are being hospitalized).<sup>56</sup>

In general, cohort studies provide more evidence for a causal relationship between exposure and outcome and can often study many exposure-outcome relationships with less chance for bias and confounding than case-control studies if the design, conduct, data collection and analysis are proper. However, cohort study designs also remain susceptible to certain types of bias and confounding, and cohort studies are often very expensive, take a long time to conduct, and may be difficult to perform, especially if the outcome of interest is rare.

Plaintiffs' epidemiologists repeatedly downplay the results of the four relevant cohort studies. Dr. McTiernan, for example, has the opinion that there are a number of "serious limitations" in the cohort studies, including that they were not specifically designed to investigate the relationship between talc use and ovarian cancer, but rather examined a number of different outcomes.<sup>57</sup> This point is irrelevant as cohort studies are designed specifically to have the ability to investigate many exposure-outcome relationships, even if the cohort study was not specifically designed to look at the exposure-outcome relationship of interest. Dr. McTiernan also criticizes the cohort studies on other grounds – that they did not obtain detailed lifetime histories of talcum powder use and therefore could not measure dose-response; that the sample sizes were too small to detect a relative risk like 1.24; and that the latency period of ovarian cancer makes these studies "not likely reflective of risk from exposure to talcum powder products."<sup>58</sup> But as just explained, no type of study in this context can provide an accurate measure of dose-response due to the problems inherent in relying on study participants' subjective assessments regarding the amount of talcum powder they use, and as I elaborate in part VIII.A below, Dr. McTiernan's criticisms with respect to latency and sample size are speculative and wrong. All of this suggests that Dr. McTiernan's criticisms reflect her own bias. While cohort studies also have their own limitations like any other study design, the focused criticism of cohort studies by plaintiffs' epidemiologists, even though they are generally considered more reliable than case-control studies, suggests a biased approach to their analyses.

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<sup>56</sup> Oleckno, *Epidemiology: Concepts and Methods*. (2008) at 207; Infante-Rivard, *Hospital or Population Controls for Case-Control Studies of Severe Childhood Diseases?* (2003) 157(2) Am J Epidemiol 176.

<sup>57</sup> McTiernan Report 46.

<sup>58</sup> *Id.* at 46-47.

## ***F. Meta-Analysis***

Gross et al.<sup>59</sup> in 1995 reviewed nine case-control studies (all previously described above) and one cohort study to evaluate the association between talc and ovarian cancer. The authors combined the results of seven studies and found an increase in risk of ovarian cancer (RR: 1.20; 95% CI: 1.01-1.44) with any talc exposure, and combined the results of five studies and, after adjustment, found an increase in risk of ovarian cancer (RR: 1.29; 95% CI: 1.02-1.63). Unfortunately, there is little detail provided regarding the methods used to identify, evaluate and analyze the studies, making the interpretation of this investigation challenging and problematic. In addition, all of the limitations described above with respect to the included case-control studies remain inherent within this investigation.

Huncharek et al.<sup>60</sup> in 2003 evaluated 15 case-control studies (all previously described above) and one cohort study using a predefined technique for literature search, study inclusion and analysis. The study included data from 11,933 subjects and pooling all subjects demonstrated a summary OR of 1.33 (95% CI: 1.16-1.45) for ovarian cancer with being exposed to never versus ever talc, none versus any talc and never versus any talc. Seven studies analyzed together yielded an inverse relationship between duration of exposure and ovarian cancer, with low-exposure groups having a higher risk and high-exposure groups having a lower risk, demonstrating a lack of clear dose-response. Hospital-based case-control studies demonstrated no significant relationship between talc use and risk of ovarian cancer (RR: 1.19; 95% CI: 0.99-1.41), while population-based case-control studies showed an increased risk of ovarian cancer with talc use (RR: 1.38; 95% CI: 1.25-1.52). As mentioned above, the limitations of the previously described case-control studies remain inherent within this review. Furthermore, differences in recall bias between hospital-based and population-based case-control studies provide one possible explanation for differences found between the two different study designs.

Huncharek et al.<sup>61</sup> in 2007 evaluated nine case-control studies (all previously described above) investigating the association between talc via dusting of contraceptive diaphragms and ovarian cancer in 2,281 cases of ovarian cancer and 3,608 controls using a predefined technique for literature search, study inclusion and analysis. Pooling all subjects demonstrated no significant risk of ovarian cancer with being exposed to talc via dusting of contraceptive diaphragms (OR 1.03; 95% CI: 0.80-1.37). One included case-control study did not explicitly provide data on talc use via contraceptive diaphragms, and without data from this study, the resultant OR was 1.12 (95% CI: 0.84-1.48).<sup>62</sup>

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<sup>59</sup> Gross & Berg, *A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer*. (1995) 5(2) J Expo Anal Environ Epidemiol. 181.

<sup>60</sup> Huncharek et al., *Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from Sixteen Observational Studies*. (2003) 23 Anticancer Res. 1955.

<sup>61</sup> Huncharek et al., *Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies*. (2007) 18 Eur J Cancer Prev 422.

<sup>62</sup> Dr. Zambelli-Weiner has criticized the Huncharek studies and did indeed find some errors in them. However, her analysis did not show that any errors materially affected the conclusions of these studies.

Langseth et al.<sup>63</sup> in 2008 reported on a meta-analysis of 20 case-control studies and make reference to one cohort study. Results were separated into 14 population-based case-control studies and six hospital-based case-control studies. The investigators state that the cohort study showed “no association between cosmetic talc use and risk of all subtypes of ovarian cancer combined,” although the results were not shown. The hospital-based case-control studies reported a pooled odds ratio of 1.12 (95% CI: 0.92-1.36) and the population-based case-control studies reported a pooled odds ratio of 1.40 (95% CI: 1.29-1.52). The combined OR from all case-control studies using a fixed effects model was 1.35 (95% CI: 1.26-1.46). This meta-analysis reflects some methodological weaknesses, including the fact that there is no report of a literature search strategy and no structured review of the literature for eligible studies.

Berge et al.<sup>64</sup> in 2018 reported on a meta-analysis of 27 studies, which included 24 case-control studies and three cohort studies. The authors reported a “small increased risk” with a summary relative risk of 1.22 (95% CI: 1.13-1.30) for ever talc use and ovarian cancer, but found that the cohort studies did not show an association (RR 1.02 (95% CI: 0.85-1.20)). The investigators demonstrated that given the total number of exposed and unexposed cases of ovarian cancer, the statistical power of the cohort studies to detect a relative risk difference of 1.25 was 0.99, which matched that of the case-control studies, and thus rejected inadequate power as an explanation for the lack of an association between talc exposure and ovarian cancer in the cohort studies and the heterogeneity between study designs. The study found a “weak trend in RR with duration and frequency of genital talc use,” but cautioned that this analysis was based on few studies and that the “modest association between both duration and frequency of use of talc may reflect a true relationship, or recall bias or confounding.” The authors noted that several aspects of their analysis, including heterogeneity between case-control and cohort studies, did “not support a causal interpretation of the association.”

Penninkilampi et al.<sup>65</sup> in 2018 reported on a meta-analysis of 24 case-control studies and three cohort studies. The study reported a summary odds ratio of 1.31 (95% CI: 1.24, 1.39) for any talc use and ovarian cancer, but this association was not present in cohort studies (OR 1.06 (95% CI: 0.90-1.25)). Although the study reported a statistically significant association in the cohort studies for serous invasive ovarian cancer (OR 1.25 (95% CI: 1.01, 1.55)), it excluded the 2010 Gates study from its analysis. The study further found that more than 3,600 lifetime talc applications “were slightly more associated with ovarian cancer than” fewer than 3,600 lifetime applications (odds ratios of 1.42 and 1.32, respectively), but noted that these data came from case-control studies and were therefore “prone to recall bias” (which the study observed could be particularly problematic due to recent media coverage of talc lawsuits). It also observed that the “mechanism by which perineal talc use may increase the risk of ovarian cancer is uncertain,” and in particular that use of NSAIDs “is not inversely associated with the incidence of ovarian cancer, as may be

<sup>63</sup> Langseth et al., *Perineal use of talc and risk of ovarian cancer*. (2008) 62 J Epidemiol Community Health 358.

<sup>64</sup> Berge et al., *Genital use of talc and risk of ovarian cancer: a meta-analysis*. (2018) 27 Eur J Cancer Prev 248.

<sup>65</sup> Penninkilampi and Eslick, *Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis*. (2018) 29(1) Epidemiology 41.

expected if the etiology was related to chronic inflammation.” The authors cited the “substantial need for further research on a potential mechanism” as one reason why a causal relationship could not be established with any certainty.

In summary, the published meta-analyses have been of varying quality and in general observed a weak association (odds ratio roughly 1.3) between talc use and ovarian cancer. However, as the meta-analyses have noted, the observed increased risk is restricted entirely to case-control studies and may be a result of bias and/or confounding. Although different studies employ different techniques to attempt to adjust for these issues, meta-analyses are only as good as their underlying studies, and the fact that the meta-analyses themselves combine studies that used different adjustment approaches can exacerbate issues regarding overall reliability.

## VII. ANALYSIS OF STUDIES

It is my opinion that there is insufficient evidence to support a causal association between exposure to talc and risk of ovarian cancer based on the body of available epidemiologic observational studies that have been performed and reported in the literature. While there is no single method for undertaking a causal assessment based on epidemiology, the criteria formulated by Austin Bradford Hill are often used and are considered the gold standard for evaluating causation once an association has been identified. These include: strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimentation and analogy.<sup>66</sup> While Bradford Hill suggests nine different viewpoints to consider in a careful examination of the association between exposure and outcome before concluding that a causal relationship exists, it is important to understand that none of his concepts provide unquestionable evidence for or against a causative relationship and none is required as essential or absolutely necessary. They can simply help to provide a framework to guide epidemiologists to decide whether or not there is another more likely way of explaining the association, including non-causal explanations for the results of individual studies. These other explanations can come from bias, confounding and/or random error (as discussed above), can lead to risk estimates that are falsely higher or lower than actual risk and can even lead to conclusions that an exposure causes disease when it does not.

Even before starting such an analysis, however, one should examine whether the epidemiologic literature establishes a true association – the fundamental predicate of a Bradford Hill analysis. As Hill noted in his seminal article setting forth his epidemiologic approach, before evaluating causation, studies must “reveal an association between two variables, *perfectly clear-cut and beyond what we would care to attribute to the play of chance*.”<sup>67</sup> As I discuss further below, this requirement is likely not satisfied here because we are not presented with a “clear cut” association.

A number of the Hill factors further weigh decidedly against a causal finding in this instance. In particular, and as detailed in this section, lack of consistent results among studies, lack of reliable assessment of exposure to talc, lack of a dose-response relationship

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<sup>66</sup> Hill, *Environment and disease: association or causation?* (1965) 58 Proc Royal Soc Med. 295.

<sup>67</sup> *Id.*

and lack of strength of association all contribute to my opinion that there is a lack of reliable evidence to conclude that exposure to talc increases the risk of ovarian cancer.

***A. Lack Of Consistency Between Studies***

One of the most striking aspects of the studies is their inconsistency.

Some studies demonstrate an association between talc use and ovarian cancer, while others do not. As set forth in the table below, there are seven hospital-based case-control studies that consistently demonstrate no statistically significant association between exposure to talc and risk of ovarian cancer. There are four cohort studies that also consistently demonstrate no statistically significant association between exposure to talc and risk of ovarian cancer. There are 26 population-based case-control studies that demonstrate inconsistent results, with some studies demonstrating a statistically significant association between exposure to talc and risk of ovarian cancer, while others demonstrate no statistically significant association between exposure to talc and risk of ovarian cancer. This lack of consistency in finding a statistically significant association between talc use and risk of ovarian cancer likely arises from several factors. The studies use varying questionnaires, describe varying self-reported assessments of talc exposure and varying self-reported assessments of frequency and duration of talc use, and apply no adjustment or varying levels of adjustment for potential confounders. Finally, each one of these observational studies has limitations (recall bias and confounding in case-control studies; lack of repeated measure of exposure in cohort studies). The consistency of effect between hospital-based case-control studies and the cohort studies is somewhat assuring and the heterogeneity among population-based case-control studies weigh against finding a causal relationship between exposure and outcome. In addition, even though the methods for at least two of the reported meta-analyses were relatively robust, the studies that were used in all of the meta-analyses were of limited quality.

***B. Lack Of Reliable Assessment Of Talc Exposure***

In all of the studies investigating the possible causal association between talc and ovarian cancer, assessment of talc exposure relies on self-report. Talc use is not documented in a medical record or in a pharmacy record in order to confirm, or at least verify, self-reported use. This has a substantial potential to lead to recall and reporting bias, in particular in case-control studies, although this type of bias may also be present in cohort studies. Furthermore, self-reported exposures were obtained from responses to questionnaires on the use of talc or talc products, including: use of talc, diaphragm with talc, diaphragm storage only, all over body talc, genital talc, legs only talc, non-genital talc, talcum powder in the perineum, talcum powder on sanitary pads, talcum powder on diaphragms, “genital fiber use”, after bathing only, baby powder only, deodorizing powder, dusting powder to the perineum, any dusting powder, talc around the abdomen/ perineum, perineal dusting, genital powder application, genital/rectal talc, powder to genitals, powder to diaphragm, or powder to sanitary napkins. Varying amounts of talc exist within different powders, varied methods can be used to apply talc either by spray or by powder, varying amounts may be applied on diaphragms, and the amount applied may be very different depending on the method of application and the person applying it. Questions arise, such as: How much talc is used in dusting? How much talc is used in the perineum? How much

talc is used after bathing only, etc.? In addition, there are no observational studies or meta-analyses that have investigated the effect of a standardized amount of talc usage or a standardized method of use to ensure consistency of the assessment of exposure. As an epidemiologist, I find this lack of ability to quantify a dose to be a gaping hole in the exposure-outcome relationship and a tremendous limitation in all of the epidemiologic studies evaluating talc and risk of ovarian cancer.

### ***C. Lack Of A Dose-Response To Talc Exposure***

There have been very few case-control studies and no cohort studies that have reported a dose-response relationship between talc exposure and risk of ovarian cancer; and measures of dose-response generally have varied widely among studies.

Dose-response curves may increase with increasing exposure (i.e., increased risk of heart disease with increasing level of cholesterol) and decrease with increasing exposure (i.e., decreased risk of heart disease with increased doses of cholesterol lowering agent). Typically, a dose-response curve that depicts an increased risk would demonstrate increasing risk with increasing quantity of exposure, increasing frequency of exposure, increasing duration of exposure or a combination. When the curve is concave, convex or has a haphazard random shape, that is a red flag to epidemiologists. Studies that have evaluated the potential for dose-response have found: (1) random or “sine wave” (up and down) risk<sup>68</sup>; (2) convex (up then down) risk<sup>69</sup>; (3) concave (down then up) risk<sup>70</sup>; and (4) even decreasing risk<sup>71</sup> with either increasing frequency or duration of talc use. Studies by Wu<sup>72</sup> and Cramer<sup>73</sup> demonstrated increasing risk of ovarian cancer with increasing frequency and duration of reported talc use, but not all cut-offs were statistically significant. Only one study<sup>74</sup> demonstrated a statistically significant association between duration of reported talc use (per five years of reported genital talc use) and risk of ovarian cancer in Hispanics (OR: 1.18; 95% CI: 1.02-1.36) and non-Hispanic whites (OR: 1.14; 95% CI: 1.08-1.21).

In sum, the vast majority of both case-control and cohort studies demonstrate no statistically significant dose-response relationship between talc use and risk of ovarian cancer.

### ***D. Lack Of Strength Of Association***

Another indicator of causality is strength of association.

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<sup>68</sup> Booth (1989); Wong (1999); Cook (1997); Mills (2004); Merritt (2008); Gertig (2000).

<sup>69</sup> Cramer (1999); Chang (1997); Cramer (2016); Rosenblatt (2011); Houghton (2014).

<sup>70</sup> Whittemore (1988); Gates (2008).

<sup>71</sup> Hartge (1983).

<sup>72</sup> Wu (2009).

<sup>73</sup> Cramer (2016).

<sup>74</sup> Wu (2015).

Relative risk and odds ratios are two measures of strength of association. The higher the relative risk or odds ratio, the greater the likelihood that the relationship is causal. For instance, the International Primary Pulmonary Hypertension Study was a case-control study where cases were defined as patients with pulmonary hypertension without a known reason.<sup>75</sup> Controls were randomly selected from lists of consecutive patients seen by the same general practitioner. Each participant went through a face-to-face interview and was asked about demographics, medical and surgical history as well as medication history. Use of appetite suppressants was associated with a statistically significant increase in risk of pulmonary hypertension (OR: 6.3; 95% CI: 3.0-13.2) after adjusting for systemic hypertension, use of cocaine or intravenous drugs, smoking status, BMI, weight loss behavior, use of thyroid extracts and possible exposure to anorexic agents. The odds ratio in this study was found to be 6.3, and with a relative risk this high it is unlikely that any other factor could be the cause of the association.

The higher the relative risk or odds ratio, the less likely other factors can explain the association. Similarly, for relative risks or odds ratios that are lower, it is important to understand that there may be factors other than the exposure of interest that can explain the association. Rosenblatt (1998)<sup>76</sup> found a statistically significant association between women who had ever douched and those who used powder in the perineal area (OR: 2.9; 95% CI: 1.6-5.1). Gonzalez et al.<sup>77</sup> as described above evaluated the effect of douching and talc use on the risk of ovarian cancer prospectively in the Sister Study. Results demonstrated no statistically significant increased risk of ovarian cancer (HR: 0.73; 95% CI: 0.44-1.2) with ever talc use when compared with never talc use after adjusting for confounders. However, there was a statistically significant increase in risk of ovarian cancer (HR: 1.9; 95% CI: 1.2-2.9) with douching/no talc use when compared with neither use as well as a statistically significant increase in risk of ovarian cancer with douching in the past 12 months (HR: 1.84; 95% CI: 1.2-2.8) when compared with never douching. As previous studies (except for Harlow et al. (1992)) did not account for douching, the relatively weak statistically significant associations could potentially be explained by confounding. One explanation could be that since talc users are more likely to douche and douching appears to increase risk of ovarian cancer, previous studies may not have captured the correct exposure (douching) in the causal pathway and mistakenly concluded talc to be the exposure that increased risk of ovarian cancer instead of douching. Similarly, it is also possible that the relatively weak yet statistically significant associations seen in some of the case-control studies could be explained by other potential confounders that were only considered in some of the studies or that have not yet even been identified.

In summary, based on evidence in the literature and the lack of consistency across studies, the lack of a reliable assessment of actual talc exposure, the lack of a significant dose-response to talc exposure, and a weak strength of association between a poorly characterized exposure to talc and risk of ovarian cancer, it is impossible to conclude that talc exposure increases the risk of ovarian cancer.

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<sup>75</sup> Abenham et al., *Appetite-Suppressant Drugs and the Risk of Primary Pulmonary Hypertension*. (1996) 335(9) N Engl J Med 609.

<sup>76</sup> Rosenblatt (1998).

<sup>77</sup> Gonzalez (2016).

Author	Odds Ratio/Relative Risk/Hazard Ratio	95% CI	Statistically Significant Association?
<b>Hospital-based case-control studies</b>			
Hartge et al. (1983)	0.70	0.04-1.10	No
Whittemore et al. (1988)	1.45	0.81-2.60	No
Booth et al. (1989)	1.30	0.80-1.90	No
Rosenblatt et al. (1992)	1.70	0.70-3.90	No
Tzonou et al. (1993)	1.05	0.28-3.98	No
Hartge and Stewart (1994)	0.30 (5-9 years of talc exposure) 0.50 (10+ years)	0.10-1.40 0.20-1.50	No
Wong et al. (1999)	1.13	0.88-1.44	No
<b>Population-based case-control studies</b>			
Cramer et al. (1982)	1.92	1.27-2.89	Weak
Harlow and Weiss. (1989)	1.10	0.70-2.10	No
Harlow et al. (1992)	1.50	1.00-2.10	Weak
Chen et al. (1992)	3.90	0.90-10.6	No
Cramer and Xu (1995)	1.60	1.20-2.10	Weak
Purdie et al. (1995)	1.27	1.04-1.54	Weak
Green et al. (1997)	1.30	1.10-1.60	Weak
Shushan et al. (1996)	1.97	1.06-3.66	Weak
Chang and Risch (1997)	1.42	1.08-1.86	Weak
Cook et al. (1997)	1.60	0.90-2.80	No
Godard et al. (1998)	2.49	0.94-6.58	No
Cramer et al. (1999)	1.60	1.18-2.15	Weak
Ness et al. (2000)	1.50	1.10-2.00	Weak
Mills et al. (2004)	1.37	1.02-1.85	Weak
Pike et al. (2004)	1.60	1.18-2.18	Weak
Jordan et al. (2007)	1.00	0.40-2.10	No
Gates et al. (2008)	1.36	1.14-1.63	Weak
Merritt et al. (2008)	1.17	1.01-1.36	Weak
Moorman et al. (2009)	Afr. Am.: 1.19 Caucasian: 1.04	Afr. Am: 0.68-2.09 Caucasian: 0.82-1.33	No
Wu et al. (2009)	1.53	1.13-2.09	Weak
Rosenblatt. (2011)	1.27	0.97-1.66	No
Kurta et al. (2012)	1.40	1.16-1.69	Weak
Wu et al. (2015)	1.46	1.27-1.69	Weak
Schildkraut et al. (2016)	1.44	1.11-1.86	Weak
<b>Pooled case-control studies</b>			
Terry et al. (2013)	1.24	1.15-1.33	Weak

Author	Odds Ratio/Relative Risk/Hazard Ratio	95% CI	Statistically Significant Association?
Cramer et al. (2016)	1.33	1.16-1.52	Weak
<b>Cohort studies</b>			
Gertig et al. (2000)	1.09	0.86-1.37	No
Gates et al. (2010)	1.06	0.89-1.28	No
Houghton et al. (2014)	1.12	0.92-1.36	No
Gonzalez et al. (2016)	0.73	0.44-1.20	No

## VIII. METHODOLOGICAL FLAWS IN PLAINTIFFS' EXPERTS' EPIDEMIOLOGY-BASED OPINIONS

I was asked to address whether the causation analyses set forth in the expert reports of plaintiffs' epidemiology experts were conducted in a scientifically reliable manner. As set forth below, I have concluded that there are several significant methodological flaws that are prevalent in multiple plaintiffs' experts' reports, rendering their analyses unreliable.

### *A. Disregard For The Hierarchy Of Evidence*

The hierarchy of evidence is well-established within the scientific community.<sup>78</sup> Consistent with that hierarchy, epidemiologists consider meta-analyses of multiple randomized clinical trials, followed by individual randomized clinical trials, as the strongest evidence to support a causal relationship between an exposure and an outcome. These are followed by the observational designs, with cohort studies, case-control studies, and cross-sectional studies in descending order also providing potential evidence for a causal association between exposure and outcome. The lowest quality of evidence comes from case reports, case series and other descriptive studies. As a general rule, lower-quality studies provide less information on whether a causal relationship exists than studies of higher quality.

Although this hierarchy should not be indiscriminately applied to all research questions and studies, an epidemiologist should provide sound scientific justifications for departing from these well-established norms. For example, a poorly designed and conducted meta-analysis or randomized clinical trial may provide less evidence than a well-designed and conducted cohort or case-control study.

A number of plaintiffs' epidemiologists ignore the well-established hierarchy of evidence in their reviews of the relevant human studies, either by treating all studies equally or, even more troublingly, placing an inappropriate amount of weight on case-control studies that they claim demonstrate a weak association between talc use and ovarian cancer, while ignoring stronger, better designed cohort studies that do not show any association and also better capture the temporal nature that must exist to demonstrate a causal relationship

<sup>78</sup> Nat. Health & Medical Res. Council, *NHMRC Levels of Evidence and Grades for Recommendations for Developers of Clinical Practice Guidelines* (2009).

between exposure and outcome. For example, Dr. Moorman states the following in her report:

As I evaluated individual epidemiologic studies (case-control and cohort studies) that described the risk for ovarian cancer associated with talc use, I did not weight one design more heavily than the other because there are advantages and disadvantages to each design for evaluating talc as a cause of ovarian cancer.<sup>79</sup>

Likewise, Dr. McTiernan states in her report that “all” studies provide evidence of causal effect.<sup>80</sup> When asked at her deposition about the hierarchy of scientific evidence, Dr. McTiernan testified that she was “not sure what hierarchy” the questioner was referring to and that, in any event, “depending on the question, one type of study could be preferable to another, but in general all of the studies provide information, and we look at the totality of evidence.”<sup>81</sup> When I teach students about study design in epidemiology, this is exactly what I tell them *not* to do. When evaluating whether causality can be demonstrated from a particular study or series of studies, it is essential to evaluate the strengths and potential weaknesses of each individual study. Because case-control studies are more easily subject to biases and confounding factors and can often not fully capture the temporal relationship between exposure and outcome, as discussed in detail below, they are often less reliable than cohort studies.

Even more problematic than treating all studies the same is plaintiffs’ experts’ tendency to place *more* emphasis on case-control studies than higher-quality cohort studies, despite their limitations. For example, despite her disclaimer of adherence to any hierarchy of evidence, Dr. McTiernan does apply a hierarchy of her own, suggesting that case-control studies are preferable in situations where an exposure is “very difficult to measure and which can change over time.”<sup>82</sup> While I agree with her that case-control studies are often “easier” when an exposure may be “difficult to measure,”<sup>83</sup> a poor-quality case-control study does not provide higher quality data due to limitations in design. Furthermore, case-control studies, as mentioned above, can be subject to bias and confounding, even when they are well designed. Even though case-control studies sometimes may be “easier” to conduct, the temporal relationship between exposure and outcome is often more difficult to establish because ascertainment of the exposure is done after the outcome. Finally, it is often extremely difficult for a case-control study design to accurately investigate an exposure that changes over time and a cohort design will more likely be able to investigate time varying exposures than a case-control study design. Dr. McTiernan’s suggestion therefore is illogical, and in my opinion, is not supported by any science.

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<sup>79</sup> Moorman Report 10.

<sup>80</sup> McTiernan Report 18.

<sup>81</sup> McTiernan Deposition 118.

<sup>82</sup> McTiernan Deposition 117.

<sup>83</sup> *Id.*

Dr. McTiernan has also criticized the multiple cohort studies finding no association between talc use and ovarian cancer on the ground that those studies involved an “insufficient number of cases . . . to find a statistically significant result.”<sup>84</sup> Dr. McTiernan’s criticism seems to be that, because ovarian cancer has a low incidence rate – and so few study participants developed the disease in both the study and control populations – the studies cannot rule out the possibility of a link between talc use and ovarian cancer. This position is incorrect.

The first problem with Dr. McTiernan’s criticism is that her focus on the low overall incidence of ovarian cancer in the population is misplaced. Incidence rates reported by the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program are estimated rates for *all* women. These rates may change from year to year, and rates may be different for different age groups and races as reported by SEER.<sup>85</sup> Observational studies do not study the population at large, but rather a subset of the population (i.e., study participants). And the incidence of ovarian cancer in the population enrolled in the cohort studies, including Gonzalez (2016) (41,654 women),<sup>86</sup> Houghton (2014) (61,576 women),<sup>87</sup> and Gates (2010)/Gertig (2000) (108,870 women),<sup>88</sup> was higher than in the general population, with 429 cases among 68,435 participants who reported exposure to talc, and 943 cases among 141,345 participants who reported no exposure to talc. It is not surprising that the incidence rates of ovarian cancer in the cohort studies are much higher than the reported rates for all females by the SEER Program because the cohort studies may include women who are in general at higher risk of developing ovarian cancer (i.e., older age, family history of cancer etc.).

A higher incidence of disease in the study population means that the number of participants needed to detect true risk is decreased – i.e., smaller sample sizes can detect the same amount of risk. Thus, because the cohort studies involve women who likely have a higher risk of ovarian cancer than the general population as reported by SEER, the study sample sizes needed to detect a given difference in risk between groups will be smaller. (This is why epidemiologists study higher-risk groups for less-common disease.) Specifically, using the Berge study’s meta-analysis of cohort studies,<sup>89</sup> which concluded that combined cohort studies yielded no increased risk of ovarian cancer when comparing participants exposed to talc to participants not exposed to talc (RR: 1.02; 95% CI: 0.85-1.20), I calculated that the incidence of ovarian cancer and the overall number of study participants was sufficient to detect a true risk of ovarian cancer of 1.25 with a power of .99.<sup>90</sup> In other words, there would be a 1% chance of being incorrect and concluding that there is no difference in risk of ovarian cancer between participants exposed and unexposed to talc if there was a true increase in risk of ovarian cancer with talc exposure.

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<sup>84</sup> McTiernan Deposition 124.

<sup>85</sup> <https://seer.cancer.gov/statfacts/html/ovary.html>.

<sup>86</sup> Gonzalez (2016).

<sup>87</sup> Houghton (2014).

<sup>88</sup> Gates (2010); Gertig et al., *Prospective Study of Talc Use and Ovarian Cancer*. (2000) 92 J. Nat. Cancer Inst. 249.

<sup>89</sup> Berge 2018.

<sup>90</sup> Calculations performed with STATA SE 15.1, StataCorp, College Station, TX.

Dr. Moorman's power-based criticisms are similarly flawed. She relies on commentary by Narod,<sup>91</sup> who states that "the lack of a significant overall association between ever use of talc and ovarian cancer in the cohort studies may be due to the fact that despite the large size of the cohorts, the studies were not adequately powered to detect a relative risk of approximately 1.2." But this commentary rests on sample size calculations with certain assumptions regarding risk of ovarian cancer, including the same incidence rate issue that undermines Dr. McTiernan's critique. When the actual incidence rate of ovarian cancer in the cohort studies is taken into account, it decreases the study sample size needed to the sample sizes reported in the relevant cohort studies.

Relatedly, the fact that so few participants in Gonzalez (2016),<sup>92</sup> Houghton (2014),<sup>93</sup> and Gates (2010)/Gertig (2000),<sup>94</sup> developed ovarian cancer regardless of their talc exposure does not undermine the validity of these studies. To the contrary, it demonstrates that the risk of developing ovarian cancer is small among the higher-risk populations that were studied, and that talc exposure simply does not increase that risk to a statistically significant degree.

Other plaintiffs' experts have criticized cohort studies on the grounds that they do not sufficiently account for the latency period of ovarian cancer. For example, Dr. Siemiatycki has stated that the "short follow-up periods in cohort studies would be a source of bias."<sup>95</sup> According to Dr. Siemiatycki, because cohort study researchers "collect information about exposure, and then follow [patients] for two years to find out how many of them got cancer, and whether there is a difference between the people who were exposed and the people who are not exposed, well, that would be pretty hopeless because it takes more than two years for cancers to develop and be diagnosed."<sup>96</sup> But this supposed limitation on cohort studies is greatly exaggerated. Houghton (2014) asked about talcum powder use in study participants who had been followed for up to 18 years and found no statistically significant increased risk in ovarian cancer.<sup>97</sup> Gates (2010) added to the Gertig (2000) cohort and followed study participants for up to 24 years and found no statistically significant elevations in risk for talc use for all epithelial ovarian cancers.<sup>98</sup> Similarly, Gonzalez (2016) followed participants with a sister or half-sister with a history of breast cancer for a median 6.5 years and found no association between the use of talc and ovarian cancer.<sup>99</sup> In any event, the women followed in all of these studies presumably did not start

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<sup>91</sup> Narod, *Talc and ovarian cancer*. (2016) 141 Gynecol. Oncol. 410. Plaintiffs' experts Drs. Ellen Blair Smith and Judith Wolf place similar reliance on Narod's commentary on the power of cohort studies to detect risk. (Blair Smith Rep. at 20; Wolf Rep. at 6.)

<sup>92</sup> Gonzalez (2016).

<sup>93</sup> Houghton (2014).

<sup>94</sup> Gates (2010); Gertig et al., *Prospective Study of Talc Use and Ovarian Cancer*. (2000) 92 J. Nat. Cancer Inst. 249.

<sup>95</sup> Siemiatycki Deposition 171.

<sup>96</sup> *Id.*

<sup>97</sup> Houghton (2014).

<sup>98</sup> Gates (2010); Gertig (2000).

<sup>99</sup> Gonzalez (2016).

using talc for the first time the day the studies began and therefore would have had longer durations of use than the time period of the study – in most cases many years more.

***B. Ignoring Or Minimizing The Effects Of Recall Bias And Other Biases In Case-Control Studies***

Recall bias is of particular concern in retrospective case-control studies because, as compared to controls, cases “tend to search their memories to identify what might have caused their disease; healthy controls have no such motivation.”<sup>100</sup> This, in turn, tends to artificially increase the supposed effect of the exposure. As Vetter and Mascha point out, a number of factors can affect recall bias.<sup>101</sup> Study participants with a particular disease tend to “search their memories to identify what might have caused their disease,” whereas “healthy controls have no such motivation.”<sup>102</sup> Cases tend to remember past exposures more than controls, and cases are often more likely than controls to investigate whether certain risk factors increase the risk of developing a certain disease. In addition, individuals with a disease may have greater awareness of potential risk factors for their condition or may have become sensitized by repeated physician interviews. Consider again the previous example of the investigator who is trying to determine if there is a relationship between sugary drinks and high blood pressure. If the cases tend to recall and report more sugary drink consumption simply because they have reflected more on their past experiences, recall bias could result in differential misclassification and a false overestimation of the measure of risk between the sugary drinks and high blood pressure. Because cases and controls have different incentives to recall past exposures, recall bias can lead to finding associations between exposures and diseases that do not exist. As I explained earlier, the Schildkraut case-control study demonstrates an excellent example of the effect of recall bias in assessing the effects of genital talc use before and after the year 2014.

Dr. Singh attempts to minimize this finding because “there was a statistically significant increased risk both before and after 2014.”<sup>103</sup> This is incorrect, as there is only a statistically significant association between any genital body powder use and ovarian cancer in interviews conducted after 2014, providing an exceptional real-world example of the possibility of recall bias in a case-control epidemiologic study. Likewise, Dr. McTiernan asserts that recall bias is “unlikely” to be an issue because the studies for which data collection pre-dated news reports of this association showed similar effects to those for which data were collected afterward.<sup>104</sup> However, there is no reason to believe that recall bias did not affect cases reporting perineal talc use before 2014, since there were reports of an association in the medical literature (and presumably, the media) prior to that time – and the tendency in a case-control study for cases to remember past exposures more than controls is an issue that affects case-control studies regardless of date.

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<sup>100</sup> Grimes & Schultz, *Bias and causal associations in observational research*. (2002) 259(9302) Lancet 248.

<sup>101</sup> Vetter & Mascha, *Bias, Confounding, and Interaction: Lions and Tigers, and Bears, Oh My!*. (2017) 125(3) Anesth Analg 1042.

<sup>102</sup> Grimes & Schultz (2002).

<sup>103</sup> Singh Report 45-46.

<sup>104</sup> McTiernan Report 24.

Dr. Siemiatycki also states that if recall bias were present, “we would systematically see elevated RRs from case-control studies for all manner of variables in all kinds of studies.”<sup>105</sup> This makes little epidemiologic sense, as recall bias is a known particular concern in retrospective studies that use a case-control design to investigate the association between exposure and outcome.<sup>106</sup>

### ***C. Jumping To Causation Without Sufficiently Determining Association***

Epidemiologists and other researchers are often asked to determine whether an exposure can cause an illness. As noted above, the Bradford Hill factors supply the commonly used framework for undertaking such an analysis. But as also noted above, the existence of a clear-cut, statistically significant association is a prerequisite to such an analysis. One needs to find an association between exposure and outcome first, and it is not acceptable epidemiologic methodology to apply the Bradford Hill criteria in the absence of an established association.

Plaintiffs’ experts have the opinion that “most” or the “vast majority” of the epidemiological studies show an increased relative risk of ovarian cancer for genital talc users. For example:

- Dr. Moorman states that, “among the more than two dozen studies that have reported on the association between talc use and ovarian cancer, the vast majority of them reported relative risks or odds ratios greater than one[.]”<sup>107</sup>
- Dr. Singh concludes that “[m]ost case control studies demonstrate an increased risk factor of ovarian cancer associated with talc use with an OR between 1.3 and 1.6, even after adjusting for various risk factors.”<sup>108</sup>
- Dr. Smith-Bindman pronounces that her “review of case-control studies on talcum powder use and ovarian cancer risk were consistent and indicate a 50% increase in risk of serous invasive cancer related to routine talcum powder exposure compared to no exposure.”<sup>109</sup>

The table in Section VII demonstrates that none of the hospital-based case-control studies, none of the cohort studies, and nearly half of the population-based case-control studies found no statistically significant association. Given that the association found in the literature is far from “perfectly clear-cut,” it is not clear to me that a Bradford Hill analysis is even appropriate in this situation.

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<sup>105</sup> Siemiatycki Report 54.

<sup>106</sup> Schultz & Grimes (2002).

<sup>107</sup> Moorman Report 15.

<sup>108</sup> Singh Report 53.

<sup>109</sup> Smith-Bindman Report 34 (emphasis omitted).

#### ***D. Methodological Problems With Dr. Smith-Bindman's Meta-Analysis***

One of plaintiffs' epidemiologists, Dr. Smith-Bindman, conducted her own, new meta-analysis of a portion of the talc literature for purposes of this litigation. There are significant problems with her approach that render it unreliable. The first is that the rationale for a new non-peer-reviewed meta-analysis – in an area that has already been subject to repeated meta-analyses on substantially the same body of literature – is not clearly stated. “Although this subject has hardly been studied, repeating or updating rarely (9%) leads to changes in the pooled results of meta-analyses.”<sup>110</sup> Therefore, while repeated meta-analyses should not be “discouraged a priori,” an “important question” is the “rationale for repeating the analysis” and, where the results differ from prior studies, another important question is “how [the] authors defend their conclusions in relation to prior studies.”<sup>111</sup> Dr. Smith-Bindman does not adequately do this; nor does she subject this new meta-analysis to any form of peer review – one of the cornerstones of the body of evidence contained in the medical literature. Under a section of her report that is supposed to set forth a “rationale” for her new meta-analysis, she fails to explain the methodological shortcomings of prior meta-analyses.<sup>112</sup> Instead, she asserts that she believes that “the most important research question to answer in this review is whether regular exposure to talcum powder is associated with ovarian cancer” – and serous cancer particularly – and thus that her review should be limited to those studies that supply data for “as close to approximately daily” use of talcum powder as possible.<sup>113</sup> But she does not explain why daily use is the right metric. Nor, in any event, does she actually limit her review to daily use, which, as she acknowledges, is not specifically examined in all of the studies she included in her review; and at the same time, she also excluded studies that did address daily use based on her own (unexplained) assessment that their “research methods were poorly defined.”<sup>114</sup>

Dr. Smith-Bindman reports an odds ratio of 1.43 for all ovarian cancers that is somewhat higher than prior meta-analyses,<sup>115</sup> and ultimately that the association is indicative of a causal relationship.<sup>116</sup> She does not explain why these results might be more valid and defensible in relation to prior meta-analyses, which report somewhat lower odds ratios and reach the opposite conclusion on causation. The sum total of her discussion on this is that “[t]he existing systematic reviews (in particular Penninkilampi and Berge) also concluded a significant increase in ovarian cancer risk following talcum powder exposure,”<sup>117</sup> but she fails to acknowledge that the odds ratios were lower and that neither study embraced a causal conclusion in its review of the overall scientific literature. This omission is critical. Scientists do not practice in a vacuum; they must take into account the

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<sup>110</sup> Vavken & Dorotka, *A Systematic Review of Conflicting Meta-Analyses in Orthopaedic Surgery*. (2009) 467(10) Clin Orthop Relat Res. 2723.

<sup>111</sup> *Id.*

<sup>112</sup> Smith-Bindman Report 30.

<sup>113</sup> *Id.* at 31.

<sup>114</sup> *Id.* at 32.

<sup>115</sup> *Id.* at 33.

<sup>116</sup> *Id.* at 41.

<sup>117</sup> *Id.* at 34.

entire existing body of scientific evidence. Dr. Smith-Bindman's failure to do so in any meaningful sense, as well as her failure to state the fact that there are no studies that investigated a standardized dose of talc, a standardized method of exposure to talc, or a validated assessment of the frequency and duration of talc usage, makes this a pointless exercise. Because of these fundamental flaws in her study, there is no valid basis to accept her unique perspective over the body of work of many other investigators over several decades that has reached the opposite conclusion.

A second problem with Dr. Smith-Bindman's approach concerns her treatment of serous ovarian cancer specifically. Dr. Smith-Bindman claims to have found data concerning serous ovarian cancer specifically from four studies.<sup>118</sup> But such post-hoc analyses are often speculative because identifying subgroups after the fact can be subject to problems associated with confounding. Therefore, while these analyses may be hypothesis-generating, caution is advised in interpreting the results. For instance, if weight, socioeconomic status, race or douching each were causally related to the risk of serous ovarian cancer and also related to the use of talc but were not investigated in the post-hoc analysis because the study was not designed to look at these factors, then investigators may conclude there is an association when one does not in reality exist between talc use and serous ovarian cancer.

Identifying subgroups after the fact is also inherently prone to bias because of the investigator's impressions of the results of the study.<sup>119</sup> Essentially, it allows the researcher to start with a conclusion and work backwards, which is exactly the opposite of the scientific method. And even setting aside the bias concerns in such a backwards endeavor, findings from post-hoc analyses may also be spurious because the study was not designed to address questions that are developed post-hoc, and thus, for example, no effort would have been made to match cases and controls within the subgroup.

Dr. Smith-Bindman's meta-analysis has other methodological flaws as well. For instance, Dr. Smith-Bindman stated that she alone performed "the search, according – obtaining all the papers, and then reviewing the bibliography of all those papers."<sup>120</sup> Most meta-analyses of higher quality involve more than one investigator to perform the search to decide what studies to include and what studies not to include in order to avoid bias. This was not done.<sup>121</sup> She also states that Dr. Hall helped her with "abstracting the data as a second set of eyes and in doing the statistical summary."<sup>122</sup> Based on her deposition, there also appear to be discrepancies between the numbers reported in Dr. Smith-Bindman's meta-analysis and those from the published literature, and she testified that she "was struggling to understand why the numbers and the figures were not exactly the same as the ones . . . in the published manuscript."<sup>123</sup> Dr. Smith-Bindman, as she stated in her

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<sup>118</sup> *Id.*

<sup>119</sup> Wang et al., *Statistics in Medicine – Reporting of Subgroup Analyses in Clinical Trials*. (2007) 357(21) N Engl J Med 2189.

<sup>120</sup> Smith-Bindman Deposition (Vol. I) 101.

<sup>121</sup> *Id.*

<sup>122</sup> *Id.*

<sup>123</sup> Smith-Bindman Deposition (Vol. II) 255-56.

deposition, called Dr. Hall in between the first and second part of her deposition to ask Dr. Hall “to clarify how she did the calculations of the numbers that are shown in the figures.”<sup>124</sup> These irregularities further call her meta-analysis into question.

### ***E. Methodological Errors In Plaintiffs’ Epidemiologists’ Bradford Hill Analyses***

Once an association has been established, Bradford Hill set forth a framework to help assess whether a causal relationship exists: strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experimentation, and analogy. To the extent a Bradford Hill analysis is even called for, plaintiffs’ experts took an irregular approach that seems to be results-driven. In my discussion below, I focus on three criteria – strength of association, consistency of association and biologic gradient – that are the most relevant to my opinions and experience as an epidemiologist.

#### ***1. Plaintiffs’ epidemiologists find a “strong” association where there is none.***

Strength of association measures the level of increased risk of developing a particular disease as a result of exposure to a particular substance. Strength of association is typically measured by calculating an odds ratio or relative risk – i.e., the ratio of the risk of disease in the population exposed to the risk of disease in those unexposed. A relative risk of 1.0 would indicate that there is no difference in disease risk between individuals exposed and those who are not. When the risk is low, epidemiologists typically require other strong evidence of causation.

Although there is no universal numeric definition of a “strong” association between exposure and outcome in terms of risk, it is generally accepted that ratios of risk measures between 1.1 and 2.0 represent a weak association between exposure and outcome in part because other factors (bias, confounding and random error) have the potential to explain away an apparent association of that level.<sup>125</sup> One after another, plaintiffs’ epidemiologists mischaracterize the – at best – weak association between talc use and ovarian cancer as one that is strong. For example:

- Dr. Siemiatycki states that “[*such*] a **high and significant** [relative risk] could not have occurred by chance.”<sup>126</sup>
- Dr. Singh writes that he “place[s] significant weight on the fact that studies demonstrate **a strong association** between talcum powder use and ovarian cancer[.]”<sup>127</sup>
- Dr. Moorman concludes that, “[t]aken as a whole, the **overwhelming statistical strength of these studies**, whose results are replicated over decades across a wide

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<sup>124</sup> *Id.* 255.

<sup>125</sup> Wynder et al., *Radford Conference Report: Weak associations in epidemiology and their interpretation* (3rd ed.). (1982) 11 Prev. Med. 464.

<sup>126</sup> Siemiatycki Report 63 (emphasis added).

<sup>127</sup> Singh Report 63 (emphasis added).

variety of populations and investigators, further supported by consistent meta-analysis, weighs very heavily in favor of a causal inference.”<sup>128</sup>

In his own non-peer-reviewed meta-analysis, Dr. Siemiatycki calculated the relative risk as 1.28. While I agree with Dr. Siemiatycki that a summary relative risk of 1.28, in general, represents that an exposed group has a 28% increased risk of an outcome, a relative risk in this range is weak, and may well result from bias, confounding, and/or random error rather than a true causal relationship. There is simply no disagreement about this within the scientific community. Plaintiffs’ experts’ insistence that a 1.28 relative risk is “high” raises the concern that they are pursuing a results-driven approach to their causation analysis instead of proper scientific methodology.

Furthermore, Dr. Siemiatycki states that “the statistical significance of individual studies is irrelevant to the consideration of causality; it is the totality of evidence embodied in the meta-analysis that counts.”<sup>129</sup> This might be something to consider in an ideal setting where multiple studies exist to evaluate the effect of a certain exposure that had the same design, the same conduct and the same analysis. But in this instance, in evaluating the effect of talc exposure on the risk of ovarian cancer, one cannot simply ignore the results of individual studies by lumping them together, especially when the individual studies were very different in terms of design, conduct, and analysis.

## ***2. Plaintiffs’ experts fabricate consistency by ignoring inconsistent studies.***

Plaintiffs’ experts uniformly assert that the consistency criterion has been satisfied. Dr. Singh states, for example, that “the direction and strength of association of talc and ovarian cancer is generally consistent across studies.”<sup>130</sup> Dr. McTiernan likewise concludes that “the association between use of talcum powder products and risk of ovarian cancer was highly consistent.”<sup>131</sup> I would agree with plaintiffs’ experts that there are some consistencies among the studies, but those consistencies are among hospital-based case-control studies and among large cohort studies showing no statistically significant association between talc exposure and ovarian cancer. By contrast, there are inconsistencies between hospital-based and population-based case-control studies and within population-based case-control studies. As mentioned above, there are seven hospital-based case-control studies that demonstrate no statistically significant association between talc exposure and risk of ovarian cancer, while there are 26 population-based case-control studies that show inconsistent results, with some studies demonstrating a significant effect of talc exposure on risk of ovarian cancer and others showing no significant effect of talc exposure on risk of ovarian cancer. In addition, there are four cohort studies that also demonstrate no statistically significant association between talc exposure and risk of ovarian cancer. This lack of consistency both within and between study designs suggests that any association may result from bias, confounding, and/or random error, and therefore weighs against a causal relationship.

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<sup>128</sup> Moorman Report 29 (emphasis added).

<sup>129</sup> Siemiatycki Report 63.

<sup>130</sup> Singh Report 63.

<sup>131</sup> McTiernan Report 64.

Moreover, it is important to remember (contrary to the suggestion of several of plaintiffs' experts) that for this criterion to weigh in favor of finding a causal relationship, there must be a consistency in *statistically significant* associations. Consistency in relative risks that are not statistically significant is not meaningful because that sort of consistency does not provide any degree of confidence that the claim of association made by the study is more than random chance.

### 3. *Plaintiffs' experts claim there is a dose-response where none exists.*

A causal association is far more likely if there is demonstrated biological gradient – i.e., a dose-response such that a greater dose leads to a greater risk of disease incidence rate. Almost every epidemiological study has failed to show any dose-response relationship between genital talc use and ovarian cancer as described above.<sup>132</sup> Indeed, plaintiffs' own expert Dr. Siemiatycki acknowledged in 2008 that “[t]he main epidemiological evidence against the association [between talc use and ovarian cancer] is the absence of clear exposure-response associations in most studies[.]”<sup>133</sup>

In responding to this scientific consensus, plaintiffs' epidemiologists insist that the literature supports a finding of a dose-response relationship. For example, Dr. Siemiatycki has the opinion that “there is a clear indication of increasing risk with increasing cumulative exposure” in the Terry 2013 and Schildkraut 2016 studies.<sup>134</sup> But the Terry study – which Dr. Siemiatycki calls “the most important piece of evidence we have on dose-response”<sup>135</sup> – “observed no significant trend . . . in risk with increasing number of lifetime applications.”<sup>136</sup> A significant trend was found in that study only when non-users were included in the analysis. Including individuals who are not exposed to a substance in calculating a dose-response trend is inappropriate, however, because it renders this criterion redundant of the strength-of-association inquiry. Dr. Siemiatycki dismissed the fact that the p-value for the trend is not statistically significant by suggesting that “the absence of statistical significance of the trend among the four exposed subsets is not equivalent to the demonstration of an absence of dose-response.”<sup>137</sup> That is pure speculation; if the trend line cannot be shown to be statistically significant, then there is no way to tell whether an actual relationship exists. The Schildkraut study likewise only included findings on the difference in risk between, in essence, never-users and ever-users of talc, and its analysis is therefore not relevant to a dose-response relationship.

Indeed, determining the dose of talc exposure is problematic. As Dr. Moorman acknowledges, the relevant dose of talc is not the amount applied but the amount, if any,

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<sup>132</sup> Nat. Cancer Inst., *Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ)* – Health Professional Version, [https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#link/\\_220\\_toc](https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#link/_220_toc) (last updated Jan. 4, 2019); Gonzalez (2016); Houghton (2014); Gates (2010).

<sup>133</sup> Langseth (2008).

<sup>134</sup> Siemiatycki Report 63.

<sup>135</sup> *Id.* at 45.

<sup>136</sup> Terry (2013).

<sup>137</sup> Siemiatycki Report 44.

that actually reaches the ovaries.<sup>138</sup> However, there is no validated method of evaluating the amount applied, let alone how much (if any) reaches the ovaries. As previously discussed, asking a woman how much talc she powdered on to the underwear is not something that can be objectively measured. Instead, it is inherently subjective and prone to inaccurate estimation. As also discussed above, this creates the potential for recall, reporting, and measurement bias, all of which can lead to false conclusions based on the results. For all of these reasons, the potential for inaccurate classification of exposure leads to tremendous limitations in the entire body of relevant literature, limiting the ability to conclude that there is a causal relationship between talc exposure and ovarian cancer.

## **IX. SUMMARY AND CONCLUSIONS ASSESSING CAUSALITY**

In designing an epidemiological study, the goal of a scientist is to derive findings that represent the truth in the population being studied. In this respect, choosing a study design that minimizes or eliminates the effects of bias and confounding is very important. In the context of assessing whether epidemiological studies indicate an association between genital talc use and ovarian cancer, recall bias is of particular concern among case-control studies and has demonstrably affected findings of association.

The methodologies used by plaintiffs' experts ignore fundamental principles of epidemiology. In particular, plaintiffs' experts ignore the hierarchy of evidence in evaluating studies and rely on study designs that are inherently susceptible to bias. Specifically, plaintiffs' experts pay particular attention to criticizing cohort studies, with little acknowledgment of the limitations in the case-control studies that find weak associations.

Plaintiffs' experts generally agree that even the studies that do show an association between talc use and ovarian cancer have found a relative risk in the range of 1.2-1.6. This, by definition, is a weak association. Plaintiffs' epidemiologists nonetheless characterize the association as "strong." Likewise, plaintiffs' epidemiologists try to demonstrate a dose-response relationship by relying on methodologically flawed studies and statistically insignificant trend lines. They also see consistency where the studies are inherently inconsistent.

As a professor of medicine and of public health, I have focused my career on using the science of epidemiology as a scientific tool to help improve our understanding of health and disease. The distortion of epidemiological science for purposes of litigation does not achieve those goals. Instead, it undermines scientific efforts to better understand the etiology of disease.

When analyzed in a methodological manner, the body of medical literature simply does not support the conclusion that perineal exposure to talc causes ovarian cancer.

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Moorman Report 30.

# APPENDIX A

Curriculum Vitae for Academic Promotion  
The Johns Hopkins University School of Medicine



Christian A. Merlo, M.D., M.P.H.

February 22, 2019

**DEMOGRAPHIC AND PERSONAL INFORMATION**

**Current Appointments**

2006-2015	Assistant Professor of Medicine, Johns Hopkins University School of Medicine
2009-2015	Assistant Professor of Epidemiology, Johns Hopkins University Bloomberg School of Public Health
2010-present	Associate Program Director for Scholarship, Osler House Staff Program, Johns Hopkins University School of Medicine
2014-present	Director of Outpatient Services, Johns Hopkins Division of Pulmonary and Critical Care Medicine
2015-present	Associate Program Director, Adult Cystic Fibrosis Center, Johns Hopkins Cystic Fibrosis Center
2015-present	Associate Professor of Medicine, Johns Hopkins University School of Medicine
2015-present	Associate Professor of Epidemiology, Johns Hopkins University Bloomberg School of Public Health

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**Education and Training**

Undergraduate

1992 A.B., Biology/Visual Arts, The College of The Holy Cross, Worcester, MA, *cum laude*

Doctoral/graduate

1996 M.D., Georgetown University School of Medicine, Washington, DC

2003 M.P.H., Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD

Postdoctoral

1996-1997	Intern, Internal Medicine, Georgetown University School of Medicine, Washington, DC
1997-1999	Resident, Internal Medicine, Georgetown University School of Medicine, Washington, DC
1999-2000	Chief Resident, Internal Medicine, Georgetown University School of Medicine, Washington, DC
2000-2001	Clinical Fellow, Division of Pulmonary & Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
2001-2004	Research Fellow, Division of Pulmonary & Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD

**Professional Experience:**

1999-2000 Instructor, Georgetown University School of Medicine, Washington, DC

2003-2004	Intensivist, Virginia Hospital Center, Arlington, VA
2004-2006	Instructor, Johns Hopkins University School of Medicine, Baltimore, MD
2006-2015	Assistant Professor, Johns Hopkins University School of Medicine, Baltimore, MD
2009-2015	Assistant Professor of Epidemiology, Department of Epidemiology, JHSPH
2015-present	Associate Professor, Johns Hopkins University School of Medicine, Baltimore, MD
2015-present	Associate Professor of Epidemiology, Department of Epidemiology, JHSPH

## RESEARCH ACTIVITIES

### Peer Reviewed Original Science Publications

1. Lechtzin N, John M, Irizarry R, **Merlo C**, Diette GB, Boyle MP. Outcomes of adults with cystic fibrosis infected with antibiotic-resistant *Pseudomonas aeruginosa*. *Respiration* 2006; 73: 27-33.
2. Wright JM, **Merlo CA**, Reynolds JB, Zeitlin PL, Garcia JG, Guggino WB, Boyle MP. Respiratory epithelial gene expression in patients with mild and severe cystic fibrosis lung disease. *Am J Respir Cell Mol Biol* 2006; 35: 327-336.
3. Buranawuti K, Boyle MP, Cheng S, Steiner LL, McDougal K, Fallin MD, **Merlo C**, Zeitlin PL, Rosenstein BJ, Mogayzel PJ Jr, Wang X, Cutting GR. Variants in mannose-binding lectin and tumour necrosis factor alpha affect survival in cystic fibrosis. *J Med Genet* 2007; 44: 209-214.
4. Hsu SC, Groman JD, **Merlo CA**, Naughton K, Zeitlin PL, Germain-Lee EL, Boyle MP, Cutting GR. Patients with mutations in Gsalpha have reduced activation of a downstream target in epithelial tissues due to haploinsufficiency. *J Clin Endocrinol Metab* 2007; 92: 3941-3948.
5. Kirk GD, **Merlo C**, O'Driscoll P, Mehta SH, Galai N, Vlahov D, Samet J, Engels EA. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis* 2007; 45: 103-110.
6. **Merlo CA**, Boyle MP, Diener-West M, Marshall BC, Goss CH, Lechtzin N. Incidence and risk factors for multiple antibiotic-resistant *Pseudomonas aeruginosa* in cystic fibrosis. *Chest* 2007; 132: 562-568.
7. Dasenbrook EC, **Merlo CA**, Diener-West M, Lechtzin N, Boyle MP. Persistent methicillin-resistant *Staphylococcus aureus* and rate of FEV1 decline in cystic fibrosis. *Am J Respir Crit Care Med* 2008; 178: 814-821.
8. Allen JG, Weiss ES, **Merlo CA**, Baumgartner WA, Conte JV, Shah AS. Impact of donor-recipient race matching on survival after lung transplantation: analysis of over 11,000 patients. *J Heart Lung Transplant* 2009; 28: 1063-1071.
9. **Merlo CA**, Weiss ES, Orens JB, Borja MC, Diener-West M, Conte JV, Shah AS. Impact of U.S. Lung Allocation Score on survival after lung transplantation. *J Heart Lung Transplant* 2009; 28: 769-775.
10. Weiss ES, Allen JG, Meguid RA, Patel ND, **Merlo CA**, Orens JB, Baumgartner WA, Conte JV, Shah AS. The impact of center volume on survival in lung transplantation: an analysis of more than 10,000 cases. *Ann Thorac Surg* 2009; 88: 1062-1070.
11. Weiss ES, Allen JG, **Merlo CA**, Conte JV, Shah AS. Lung allocation score predicts survival in lung transplantation patients with pulmonary fibrosis. *Ann Thorac Surg* 2009; 88: 1757-1764.
12. Weiss ES, Allen JG, **Merlo CA**, Conte JV, Shah AS. Survival after single versus bilateral lung transplantation for high-risk patients with pulmonary fibrosis. *Ann Thorac Surg* 2009; 88: 1616-25; discussion 1625-6.
13. Weiss ES, Allen JG, Modi MN, **Merlo CA**, Conte JV, Shah AS. Lung transplantation in older patients with cystic fibrosis: analysis of UNOS data. *J Heart Lung Transplant* 2009; 28: 135-140.
14. Weiss ES, **Merlo CA**, Shah AS. Impact of advanced age in lung transplantation: an analysis of United Network for Organ Sharing data. *J Am Coll Surg* 2009; 208: 400-409.
15. Allen JG, Arnaoutakis GJ, Weiss ES, **Merlo CA**, Conte JV, Shah AS. The impact of recipient body mass index on survival after lung transplantation. *J Heart Lung Transplant* 2010; 29: 1026-1033.
16. Arnaoutakis GJ, Allen JG, **Merlo CA**, Baumgartner WA, Conte JV, Shah AS. Low potassium dextran is superior to University of Wisconsin solution in high-risk lung transplant recipients. *J Heart Lung Transplant* 2010; 29: 1380-1387.
17. Dasenbrook EC, Checkley W, **Merlo CA**, Konstan MW, Lechtzin N, Boyle MP. Association between respiratory tract methicillin-resistant *Staphylococcus aureus* and survival in cystic fibrosis. *JAMA* 2010; 303: 2386-2392.
18. Drummond MB, Kirk GD, McCormack MC, Marshall MM, Ricketts EP, Mehta SH, Wise RA, **Merlo CA**. HIV and COPD: impact of risk behaviors and diseases on quality of life. *Qual Life Res* 2010; 19: 1295-1302.
19. Drummond MB, Kirk GD, Ricketts EP, McCormack MC, Hague JC, McDyer JF, Mehta SH, Engels EA, Wise RA, **Merlo CA**. Cross sectional analysis of respiratory symptoms in an injection drug user cohort: the impact of obstructive lung disease and HIV. *BMC Pulm Med* 2010; 10: 27-2466-10-27.
20. Hoag JB, Terry P, Mitchell S, Reh D, **Merlo CA**. An epistaxis severity score for hereditary hemorrhagic

- telangiectasia. *Laryngoscope* 2010; 120: 838-843.
21. Weiss ES, Allen JG, **Merlo CA**, Conte JV, Shah AS. Factors indicative of long-term survival after lung transplantation: a review of 836 10-year survivors. *J Heart Lung Transplant* 2010; 29: 240-246.
22. Allen JG, Arnaoutakis GJ, Orens JB, McDyer J, Conte JV, Shah AS, **Merlo CA**. Insurance status is an independent predictor of long-term survival after lung transplantation in the United States. *J Heart Lung Transplant* 2011; 30: 45-53.
23. Arnaoutakis GJ, Allen JG, **Merlo CA**, Sullivan BE, Baumgartner WA, Conte JV, Shah AS. Impact of the lung allocation score on resource utilization after lung transplantation in the United States. *J Heart Lung Transplant* 2011; 30: 14-21.
24. Arnaoutakis GJ, George TJ, Alejo DE, **Merlo CA**, Baumgartner WA, Cameron DE, Shah AS. Society of Thoracic Surgeons Risk Score predicts hospital charges and resource use after aortic valve replacement. *J Thorac Cardiovasc Surg* 2011; 142: 650-655.
25. Arnaoutakis GJ, George TJ, Robinson CW, Gibbs KW, Orens JB, **Merlo CA**, Shah AS. Severe acute kidney injury according to the RIFLE (risk, injury, failure, loss, end stage) criteria affects mortality in lung transplantation. *J Heart Lung Transplant* 2011; 30: 1161-1168.
26. Drummond MB, Kirk GD, Astemborski J, McCormack MC, Marshall MM, Mehta SH, Wise RA, **Merlo CA**. Prevalence and risk factors for unrecognized obstructive lung disease among urban drug users. *Int J Chron Obstruct Pulmon Dis* 2011; 6: 89-95.
27. George TJ, Arnaoutakis GJ, **Merlo CA**, Kemp CD, Baumgartner WA, Conte JV, Shah AS. Association of operative time of day with outcomes after thoracic organ transplant. *JAMA* 2011; 305: 2193-2199.
28. Marshall MM, Kirk GD, Caporaso NE, McCormack MC, **Merlo CA**, Hague JC, Mehta SH, Engels EA. Tobacco use and nicotine dependence among HIV-infected and uninfected injection drug users. *Addict Behav* 2011; 36: 61- 67.
29. Sheridan MB, Hefferon TW, Wang N, **Merlo C**, Milla C, Borowitz D, Green ED, Mogayzel PJ Jr, Cutting GR. CFTR transcription defects in pancreatic sufficient cystic fibrosis patients with only one mutation in the coding region of CFTR. *J Med Genet* 2011; 48: 235-241.
30. Tam V, Arnaoutakis GJ, George TJ, Russell SD, **Merlo CA**, Conte JV, Baumgartner WA, Shah AS. Marital status improves survival after orthotopic heart transplantation. *J Heart Lung Transplant* 2011; 30: 1389-1394.
31. West NE, Lechtzin N, **Merlo CA**, Turowski JB, Davis ME, Ramsay MZ, Watts SL, Stenner SP, Boyle MP. Appropriate goal level for 25-hydroxyvitamin D in cystic fibrosis. *Chest* 2011; 140: 469-474.
32. Drummond MB, Kirk GD, Astemborski J, Marshall MM, Mehta SH, McDyer JF, Brown RH, Wise RA, **Merlo CA**. Association between obstructive lung disease and markers of HIV infection in a high-risk cohort. *Thorax* 2012; 67: 309-314.
33. Eberlein M, Arnaoutakis GJ, Yarmus L, Feller-Kopman D, Dezube R, Chahla MF, Bolukbas S, Reed RM, Klesney-Tait J, Parekh KR, **Merlo CA**, Shah AS, Orens JB, Brower RG. The effect of lung size mismatch on complications and resource utilization after bilateral lung transplantation. *J Heart Lung Transplant* 2012; 31: 492-500.
34. George TJ, Arnaoutakis GJ, Beaty CA, Pipeling MR, **Merlo CA**, Conte JV, Shah AS. Acute kidney injury increases mortality after lung transplantation. *Ann Thorac Surg* 2012; 94: 185-192.
35. George TJ, Beaty CA, Kilic A, Shah PD, **Merlo CA**, Shah AS. Outcomes and temporal trends among high-risk patients after lung transplantation in the United States. *J Heart Lung Transplant* 2012; 31: 1182-1191.
36. Kilic A, George TJ, Beaty CA, **Merlo CA**, Conte JV, Shah AS. The effect of center volume on the incidence of postoperative complications and their impact on survival after lung transplantation. *J Thorac Cardiovasc Surg* 2012; 144: 1502-8; discussion 1508-9.
37. Kilic A, **Merlo CA**, Conte JV, Shah AS. Lung transplantation in patients 70 years old or older: have outcomes changed after implementation of the lung allocation score? *J Thorac Cardiovasc Surg* 2012; 144: 1133-1138.
38. Drummond MB, **Merlo CA**, Astemborski J, Kalmin MM, Kisalu A, McDyer JF, Mehta SH, Brown RH, Wise RA, Kirk GD. The effect of HIV infection on longitudinal lung function decline among IDUs: a prospective cohort. *AIDS* 2013; 27: 1303-1311.
39. Eberlein M, Diehl E, Bolukbas S, **Merlo CA**, Reed RM. An oversized allograft is associated with improved survival after lung transplantation for idiopathic pulmonary arterial hypertension. *J Heart Lung Transplant* 2013; 32: 1172-1178.
40. Eberlein M, Reed RM, Bolukbas S, Parekh KR, Arnaoutakis GJ, Orens JB, Brower RG, Shah AS, Hunsicker L, **Merlo CA**. Lung size mismatch and survival after single and bilateral lung transplantation. *Ann Thorac Surg* 2013; 96: 457-463.
41. Eberlein M, Reed RM, Madaa M, Bolukbas S, Arnaoutakis GJ, Orens JB, Brower RG, **Merlo CA**, Hunsicker LG.

- Donor-recipient size matching and survival after lung transplantation. A cohort study. *Ann Am Thorac Soc* 2013; 10: 418-425.
42. Kilic A, Beaty CA, **Merlo CA**, Conte JV, Shah AS. Functional status is highly predictive of outcomes after redo lung transplantation: an analysis of 390 cases in the modern era. *Ann Thorac Surg* 2013; 96: 1804-11; discussion 1811.
43. Kilic A, Shah AS, **Merlo CA**, Gourin CG, Lidor AO. Early outcomes of antireflux surgery for United States lung transplant recipients. *Surg Endosc* 2013; 27: 1754-1760.
44. Reh DD, Hur K, **Merlo CA**. Efficacy of a topical sesame/rose geranium oil compound in patients with hereditary hemorrhagic telangiectasia associated epistaxis. *Laryngoscope* 2013; 123: 820-822.
45. Yarmus L, Akulian J, Gilbert C, Illei P, Shah P, **Merlo C**, Orens J, Feller-Kopman D. Cryoprobe transbronchial lung biopsy in patients after lung transplantation: a pilot safety study. *Chest* 2013; 143: 621-626.
46. Drummond MB, Astemborski J, Lambert AA, Goldberg S, Stitzer ML, **Merlo CA**, Rand CS, Wise RA, Kirk GD. A randomized study of contingency management and spirometric lung age for motivating smoking cessation among injection drug users. *BMC Public Health* 2014; 14: 761-2458-14-761.
47. Fischer WA, Drummond MB, **Merlo CA**, Thomas DL, Brown R, Mehta SH, Wise RA, Kirk GD. Hepatitis C virus infection is not an independent risk factor for obstructive lung disease. *COPD* 2014; 11: 10-16.
48. Gashouta MA, **Merlo CA**, Pipeling MR, McDyer JF, Hayanga JW, Orens JB, Girgis RE. Serial monitoring of exhaled nitric oxide in lung transplant recipients. *J Heart Lung Transplant* 2014.
49. Hulbert A, Hooker CM, Keruly JC, Brown T, Horton K, Fishman E, Rodgers K, Lee B, Sam C, Tsai S, Weihe E, Pridham G, Drummond B, **Merlo C**, Geronimo M, Porter M, Cox S, Li D, Harline M, Teran M, Wrangle J, Mudge B, Taylor G, Kirk GD, Herman JG, Moore RD, Brown RH, Brock MV. Prospective CT screening for lung cancer in a high-risk population: HIV-positive smokers. *J Thorac Oncol* 2014; 9: 752-759.
50. Kilic A, Conte JV, Baumgartner WA, Russell SD, **Merlo CA**, Shah AS. Does recipient age impact functional outcomes of orthotopic heart transplantation? *Ann Thorac Surg* 2014; 97: 1636-1642.
51. **Merlo CA**, Yin LX, Hoag JB, Mitchell SE, Reh DD. The effects of epistaxis on health-related quality of life in patients with hereditary hemorrhagic telangiectasia. *Int Forum Allergy Rhinol* 2014; 4: 921-925.
52. Popescu I, Drummond MB, Gama L, Coon T, **Merlo CA**, Wise RA, Clements JE, Kirk GD, McDyer JF. Activation- induced cell death drives profound lung CD4(+) T-cell depletion in HIV-associated chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2014; 190: 744-755.
53. Reh DD, Yin LX, Laaeq K, **Merlo CA**. A new endoscopic staging system for hereditary hemorrhagic telangiectasia. *Int Forum Allergy Rhinol* 2014; 4: 635-639.
54. Grimm JC, Valero V 3rd, Kilic A, Crawford TC, Conte JV, **Merlo CA**, Shah PD, Shah AS. Preoperative performance status impacts perioperative morbidity and mortality after lung transplantation. *Ann Thorac Surg* 2015; 99: 482-489.
55. **Merlo CA**, Clark SC, Arnaoutakis GJ, Yonan N, Thomas D, Simon A, Thompson R, Thomas H, Orens JB, Shah AS. National health care delivery systems influence lung transplant outcomes for cystic fibrosis. *American Journal of Transplantation* 2015; Epub March 24.
56. Braun AT, Dasenbrook EC, Shah AS, Orens JB, **Merlo CA**. Impact of lung allocation score on survival in cystic fibrosis lung transplant recipients. *J Heart Lung Transplant*. 2015; Epub Jun 11.
57. Grimm JC, Valero V 3rd, Kilic A, Magruder JT, **Merlo CA**, Shah PD, Shah AS. Association Between Prolonged Graft Ischemia and Primary Graft Failure or Survival Following Lung Transplantation. *JAMA Surg*. 2015 Jun;150(6):547-53. doi: 10.1001/jamasurg.2015.12. PubMed PMID: 25874575.
58. Yin LX, Reh DD, Hoag JB, Mitchell SE, Mathai SC, Robinson GM, **Merlo CA**. The minimal important difference of the epistaxis severity score in hereditary hemorrhagic telangiectasia. *Laryngoscope*. 2015; Epub Sep 22.
59. Grimm JC, Valero V 3rd, Magruder JT, Kilic A, Dungan SP, Silhan LL, Shah PD, Kim BS, **Merlo CA**, Sciortino CM, Shah AS. A novel risk score that incorporates recipient and donor variables to predict 1-year mortality in the current era of lung transplantation. *J Heart Lung Transplant*. 2015 Nov;34(11):1449-54. doi: 10.1016/j.healun.2015.07.001. Epub 2015 Jul 22. PubMed PMID: 26275639.
60. Walker-Sperling VE, **Merlo CA**, Buckheit RW 3rd, Lambert A, Tarwater P, Kirk GD, Drummond MB, Blankson JN. HIV Controller T Cells Effectively Inhibit Viral Replication in Alveolar Macrophages. *AIDS Res Hum Retroviruses*. 2016 Aug 2. [Epub ahead of print] PubMed PMID: 27353255.
61. Mock JR, Kolb TM, Illei PB, Yang SC, Lederman HM, **Merlo CA**. Bronchus-associated Lymphoid Tissue in Kabuki Syndrome with Associated Hyper-IgM Syndrome/Common Variable Immunodeficiency. *Am J Respir Crit Care Med*. 2016 Aug 15;194(4):514-5. doi: 10.1164/rccm.201511-2305IM. PubMed PMID: 27275756.
62. Popescu I, Drummond MB, Gama L, Lambert A, Hoji A, Coon T, **Merlo CA**, Wise RA, Keruly J, Clements JE,

- Kirk GD, McDyer JF. HIV Suppression Restores the Lung Mucosal CD4+ T-Cell Viral Immune Response and Resolves CD8+ T-Cell Alveolitis in Patients at Risk for HIV-Associated Chronic Obstructive Pulmonary Disease. *J Infect Dis.* 2016 Nov 15;214(10):1520-1530. Epub 2016 Sep 9. PubMed PMID: 27613775; PubMed Central PMCID: PMC5091376.
63. Walker-Sperling VE, **Merlo CA**, Buckheit RW 3rd, Lambert A, Tarwater P, Kirk GD, Drummond MB, Blankson JN. Short Communication: HIV Controller T Cells Effectively Inhibit Viral Replication in Alveolar Macrophages. *AIDS Res Hum Retroviruses.* 2016 Oct/Nov;32(10-11):1097-1099. Epub 2016 Aug 2. PubMed PMID: 27353255; PubMed Central PMCID: PMC5067835.
64. Whitehead KJ, Sautter NB, McWilliams JP, Chakinala MM, **Merlo CA**, Johnson MH, James M, Everett EM, Clancy MS, Faughnan ME, Oh SP, Olitsky SE, Pyeritz RE, Gossage JR. Effect of Topical Intranasal Therapy on Epistaxis Frequency in Patients With Hereditary Hemorrhagic Telangiectasia: A Randomized Clinical Trial. *JAMA.* 2016 Sep 6;316(9):943-51. doi: 10.1001/jama.2016.11724. PubMed PMID: 27599329.
65. Magruder JT, Crawford TC, Grimm JC, Kim B, Shah AS, Bush EL, Higgins RS, **Merlo CA**. Risk Factors for De Novo Malignancy Following Lung Transplantation. *Am J Transplant.* 2017 Jan;17(1):227-238. doi: 10.1111/ajt.13925. Epub 2016 Aug 25. PubMed PMID: 27321167.
66. Magruder JT, Shah AS, Crawford TC, Grimm JC, Kim B, Orens JB, Bush EL, Higgins RS, **Merlo CA**. Simulated Regionalization of Heart and Lung Transplantation in the United States. *Am J Transplant.* 2017 Feb;17(2):485-495. doi: 10.1111/ajt.13967. Epub 2016 Sep 12. PubMed PMID: 27618731.
67. Drummond MB, Lambert AA, Hussien AF, Lin CT, **Merlo CA**, Wise RA, Kirk GD, Brown RH. HIV Infection Is Independently Associated with Increased CT Scan Lung Density. *Acad Radiol.* 2017 Feb;24(2):137-145. doi: 10.1016/j.acra.2016.09.019. Epub 2016 Nov 18. PubMed PMID: 27876271; PubMed Central PMCID: PMC5237394.
68. Jennings MT, Dezube R, Paranjape S, West NE, Hong G, Braun A, Grant J, **Merlo CA**, Lechtzin N. An Observational Study of Outcomes and Tolerances in Patients with Cystic Fibrosis Initiated on Lumacaftor/Ivacaftor. *Ann Am Thorac Soc.* 2017 Apr 13. doi: 10.1513/AnnalsATS.201701-058OC. [Epub ahead of print] PubMed PMID: 28406713.
69. Jennings MT, Dasenbrook EC, Lechtzin N, Boyle MP, **Merlo CA**. Risk factors for persistent methicillin-resistant *Staphylococcus aureus* infection in cystic fibrosis. *J Cyst Fibros.* 2017 Apr 23. pii: S1569-1993(17)30106-6. doi: 10.1016/j.jcf.2017.04.010. [Epub ahead of print] PubMed PMID: 28446387.
70. Crawford TC, Grimm JC, Magruder JT, Ha J, Sciortino CM, Kim BS, Bush EL, Conte JV, Higgins RS, Shah AS, **Merlo CA**. Lung Transplant Mortality Is Improving in Recipients With a Lung Allocation Score in the Upper Quartile. *Ann Thorac Surg.* 2017 May;103(5):1607-1613. doi: 10.1016/j.athoracsur.2016.11.057. Epub 2017 Feb 21. PubMed PMID: 28223052.
71. Crawford TC, Magruder JT, Grimm JC, Suarez-Pierre A, Zhou X, Ha JS, Higgins RS, Broderick SR, Orens JB, Shah P, **Merlo CA**, Kim BS, Bush EL. Impaired Renal Function Should Not Be a Barrier to Transplantation in Patients With Cystic Fibrosis. *Ann Thorac Surg.* 2017 Aug 16. pii: S0003-4975(17)30707-5. doi: 10.1016/j.athoracsur.2017.05.032. [Epub ahead of print] PubMed PMID: 28822537.
72. Reed RM, Cabral HJ, Dransfield MT, Eberlein M, Merlo CA, Mulligan MJ, Netzer G, Sanchez PG, Scharf SM, Sin DD, Celli BR. Survival of Lung Transplant Candidates With COPD: BODE Score Reconsidered. *Chest.* 2018 Mar;153(3):697-701.
73. Orens JB, Merlo CA. Selection of Candidates for Lung Transplantation and Controversial Issues. *Semin Respir Crit Care Med.* 2018 Apr;39(2):117-125.
74. Crawford TC, Lui C, Magruder JT, Ha JS, Higgins RS, Merlo CA, Kim BS, Bush EL. Five-year mortality hazard is reduced in chronic obstructive pulmonary disease patients receiving double- versus single-lung transplants. *J Surg Res.* 2018 Jun 2.
75. Hong G, Psoter KJ, Jennings MT, Merlo CA, Boyle MP, Hadjiliadis D, Kawut SM, Lechtzin N. Risk factors for persistent *Aspergillus* respiratory isolation in cystic fibrosis. *J Cyst Fibros.* 2018 Sep;17(5):624-630.
76. Crawford TC, Lui C, Magruder JT, Suarez-Pierre A, Ha JS, Higgins RS, Broderick SR, Merlo CA, Kim BS, Bush EL. Traumatically Brain-Injured Donors and the Impact on Lung Transplantation Survival. *Ann Thorac Surg.* 2018 Sep;106(3):842-847.
77. Hsu J, Krishnan A, Lin CT, Shah PD, Broderick SR, Higgins RSD, Merlo CA, Bush EL. Sarcopenia of the Psoas Muscles is Associated with Poor Outcomes Following Lung Transplantation. *Ann Thorac Surg.* 2018 Nov 14;.
78. Sharma N, Evans TA, Pellicore MJ, Davis E, Aksit MA, McCague AF, Joynt AT, Lu Z, Han ST, Anzmann AF, Lam AN, Thaxton A, West N, Merlo C, Gottschalk LB, Raraigh KS, Sosnay PR, Cotton CU, Cutting GR. Capitalizing on the heterogeneous effects of CFTR nonsense and frameshift variants to inform therapeutic strategy for cystic fibrosis. *PLoS Genet.* 2018 Nov;14(11):e1007723.

79. Fraser CD 3rd, Zhou X, Grimm JC, Suarez-Pierre A, Crawford TC, Lui C, Bush EL, Hibino N, Jacobs ML, Vricella LA, Merlo C. Size Mismatching Increases Mortality Following Lung Transplantation in Pre-Adolescent Patients. *Ann Thorac Surg*. 2019 Feb 11;.

#### Invited Reviews

1. **Merlo CA**, Boyle MP. Modifier genes in cystic fibrosis lung disease. *J Lab Clin Med* 2003;141:237-41.
2. **Merlo CA**, Orens JB. Candidate selection, overall results, and choosing the right operation. *Semin Respir Crit Care Med* 2010;31:99-107.
3. Braun AT, **Merlo CA**. Cystic fibrosis lung transplantation. *Curr Opin Pulm Med* 2011;17:467-72.
4. Kirk GD, **Merlo CA**, For the Lung HIV Study Group. HIV infection in the etiology of lung cancer: confounding, causality, and consequences. *Proc Am Thorac Soc* 2011;8:326-32.
5. Lambert AA, **Merlo CA**, Kirk GD. Human immunodeficiency virus-associated lung malignancies. *Clin Chest Med* 2013;34:255-72.

#### Inventions, Patents, Copyrights

- 2010 **Merlo CA**, Reh DR, Hoag JB. Method and severity scale for measuring epistaxis among patients with hereditary hemorrhagic telangiectasia (HHT). Used worldwide as a primary outcome in HHT interventional clinical trials.

#### Extramural Sponsorship (current, pending, previous)

##### Current Grants

- |                     |   |
|---------------------|---|
| 09/26/13 – 07/31/18 | <u>Immune Mechanisms of HIV-associated COPD</u><br>U01HL121814<br>NIH<br>\$505,539<br>PI: Gregory Kirk, MD PhD (Johns Hopkins School of Public Health)<br>Role: Co-I<br>0.60 calendar months<br>This proposal directly addresses critical gaps in our understanding of the clinical spectrum and consequences of HIV-associated COPD and will identify key biologic mechanisms contributing to the disease. Findings will inform the clinical management and development of interventions targeting HIV associated COPD, and may also inform broader strategies for COPD in non-HIV infected populations. |
| 07/01/14 – 06/30/19 | <u>Clinical Risk Factors for Primary Graft Dysfunction</u><br>R01HL087115<br>NIH subaward<br>\$19,984<br>PI: Jason Christie, MD (University of Pennsylvania)<br>Role: Co-I<br>0.12 calendar months<br>The major goal of this multicenter study is to define risk factors for the development of primary graft dysfunction following lung transplantation.   |
| 09/01/14 – 08/31/18 | <u>Predictors, consequences and mechanisms of accelerated lung aging in HIV</u><br>R01HL126549<br>NIH<br>\$499,997<br>PI: Gregory Kirk, MD PhD (Johns Hopkins School of Public Health)<br>Role: Co-I<br>0.60 calendar months<br>The goal of this program is to establish risk factors, associated co-morbidities, and immunologic and inflammatory biomarkers associated with accelerated decline in lung function in the SHIELD cohort of HIV-positive inner-city intravenous drug users.  |
| 07/01/15 – 06/30/18 | <u>Transition of Care for Patients with Cystic Fibrosis who Undergo Lung Transplantation</u><br>Spruance Foundation II Discovery Fund   |

\$300,000

PI: Christian Merlo, MD MPH

2.4 calendar months

The major goal of this proposal is to identify factors which may help to improve the process of lung transplantation for patients with cystic fibrosis.

## Previous

07/01/03 – 06/30/04

Gene Expression Analysis of Nasal Respiratory Epithelial Cells in  $\Delta F508/\Delta F508$  Individuals with Mild and Severe Cystic Fibrosis Lung Disease

Bauernschmidt Fellowship in Pulmonary Disease

Eudowood Foundation

\$35000

Role: PI

The goal of this study was to evaluate differences in gene expression between patients with cystic fibrosis with mild and severe lung disease.

07/01/04 – 06/30/07

The Effect of Multiple Antibiotic Resistant *Pseudomonas aeruginosa* on Outcomes in Cystic Fibrosis

The Harry Shwachman Clinical Investigator Award

Cystic Fibrosis Foundation

\$270000

Role: PI

6.0 calendar months

The goal of this study was to evaluate the impact of multiple antibiotic resistant *Pseudomonas aeruginosa* (MARPA) on outcomes among patients with cystic fibrosis.

07/01/06 – 06/30/07

Emphysema and HIV infection within the ALIVE cohort in Baltimore

Thomas and Carol McCann Innovative research Fund for Asthma and Respiratory Disease

\$35000

Role: Co-PI

The main goal of this study was to evaluate the association between emphysema and HIV infection among the ALIVE cohort in Baltimore.

01/01/08 – 12/30/12

The Study of HIV Infection in the Etiology of Lung Disease (SHIELD)

RFAHL07008

NIH

\$549,598

PI: Gregory Kirk, MD PhD (Johns Hopkins School of Public Health)

Role: Co-PI

0.60 calendar months

06/01/11 – 02/28/15

North American Study of Epistaxis in HHT (NOSE)

Hereditary Hemorrhagic Telangiectasia Foundation

\$11,126

Role: site PI

0.12 calendar months

This was a multicenter randomized placebo-controlled trial comparing bevacizumab, estrogen, tranexamic acid, and placebo in patients with HHT-related epistaxis.

09/06/12 – 06/30/14

Using mHealth to Respond Early to Acute Exacerbations of COPD in HIV mREACH

R34HL117349

NIH

\$376,291

PI: Gregory Kirk, MD PhD (Johns Hopkins School of Public Health)

Role: Co-I

0.60 calendar months

This clinical trial planning grant evaluated the feasibility, acceptability and defined optimal trial elements for an m-Health intervention to identify early exacerbations in HIV-COPD to improve management and clinical outcomes.

### Research Program Building / Leadership:

- 2010-present Associate Program Director for Scholarship, Osler Residency Program, Johns Hopkins University School of Medicine. In my capacity, I am responsible for the research experience for the Osler House Staff throughout residency training. This involves one on one meetings to discuss research interests and goals, an online lecture series providing an introduction to research, pairing with faculty mentors, mentorship in the presentation of research projects at local and national meetings, collecting data highlighting scholarly activity, and reporting these data to the Director for internal use as well as for ACGME purposes.
- 2010-present Director of Research, The Johns Hopkins Lung Transplant Program. In my capacity, I am responsible for coordination of research efforts within the lung transplant program. This involves multidisciplinary projects spanning across many disciplines (Medicine, Surgery, Rehabilitation, Psychology, Epidemiology) as well as across different levels of training from faculty, fellows, residents, and medical students.
- 2010-2018 Director, Hereditary Hemorrhagic Telangiectasia Center of Excellence. In my capacity, I am responsible for the coordination of multicenter clinical trials as well as local investigations among patients with HHT. Our center was responsible for creation of an epistaxis severity score (HHT-ESS), the first objective measure of epistaxis severity, now used worldwide clinically as well as an outcome measure in HHT clinical investigations.
- 2016-present Associate Director, The Johns Hopkins Adult Cystic Fibrosis Program. In my capacity, I am responsible for the coordination of aspects of clinical and research coordination for our cystic fibrosis program.
- 2016-present Director of Research, The Johns Hopkins Adult Cystic Fibrosis Program. In my capacity, I am responsible for coordination of research efforts within the Adult CF program. This involves multidisciplinary projects spanning across many disciplines (Medicine, Surgery, Psychology, Epidemiology) as well as across different levels of training from faculty, fellows, residents, and medical students.

## EDUCATIONAL ACTIVITIES

### Educational Publications

Peer-reviewed, original, educational publications – None

Review Articles – None

Editorials – None

### Case Reports

1. **Merlo CA**, Studer SM, Conte JV, Yang SC, Sonnett J, Orens JB. The course of neurofibromatosis type 1 on immunosuppression after lung transplantation: report of 2 cases. J Heart Lung Transplant 2004; 23: 774-776.
2. Houston B, Reiss KA, **Merlo C**. Healthy, but comatose. Am J Med 2011; 124: 303-305.

### Book and Book Chapters

1. **Merlo CA**, Boyle MP. "Adult Cystic Fibrosis". In The Osler Medical Handbook. Mosby. Philadelphia: 60, 899-911, 2003.
2. **Merlo CA**, Terry PB. Concise Review: Diagnosis and management of pulmonary arteriovenous malformations. In Harrison's Online. 2002. <http://www.harrisonsonline.com>.
3. **Merlo CA**, Hansel N. "Have a working knowledge of EMTALA laws as they apply to the ICU. How to be a good referring and accepting ICU physician". In Avoiding Common ICU Errors. Lippincott. 2008.
4. **Merlo CA**. Critical Care Medicine. In First Aid for the Internal Medicine Boards. McGraw-Hill. New York: 16, 123-132, 2010.

5. **Merlo CA.** Pulmonary Medicine. In First Aid for the Internal Medicine Boards. McGraw-Hill. New York: 4, 553-580, 2010.
6. Dasenbrook EC, **Merlo CA.** "Cystic Fibrosis and Bronchiectasis". In Lung Transplantation. Informa. 2010.
7. Hayes M, **Merlo CA.** "Hemoptysis". The Principles and Practice of Hospital Medicine, 1<sup>st</sup> Edition, Sylvia C. McKean, Editor-in-Chief, McGraw-Hill publishers.
8. **Merlo CA.** "Diffuse Parenchymal Lung Disease." In Current Therapy in Thoracic and Cardiovascular Surgery. Mosby 2013.
9. **Merlo CA,** Terry PB. "Chest X-Ray Review". In The Johns Hopkins Internal Medical Board Review. Mosby. 2015

**Letters, correspondence** - None

**Other Media** - None

## **Teaching**

### **Classroom instruction**

- |              |   |
|--------------|---|
| 2003-2010    | Pulmonary physiology small group facilitator, Johns Hopkins University School of Medicine, Baltimore, MD.   |
| 2003-2010    | Pulmonary pathophysiology small group facilitator, Johns Hopkins University School of Medicine, Baltimore, MD.  |
| 2004-2010    | Good Samaritan Internal Medicine Program Guest Lectures – Cystic Fibrosis, Pulmonary Function Testing, Baltimore, MD.   |
| 2004-present | Lecturer, Carol Johns Service (Inpatient Pulmonary Service) – Lecture monthly about Cystic Fibrosis and Lung Transplantation to medical students, residents, and fellows as part of the core curriculum on the inpatient pulmonary service, Johns Hopkins University School of Medicine, Baltimore, MD. |
| 2004-present | Lecturer, Pulmonary and Critical Care Medicine Fellow's Core Conference – Cystic Fibrosis, Lung Transplantation, Hereditary Hemorrhagic Telangiectasia, and Noninfectious Pulmonary Complications of HIV, Johns Hopkins University School of Medicine, Baltimore, MD.                                   |
| 2006-2014    | Chest Radiography Conference Director – Lecture weekly for 10-15 Pulmonary and Critical Care Medicine fellows regarding the reading of chest radiographs and computed tomography, Johns Hopkins University School of Medicine, Baltimore, MD.   |

### **Clinical Instruction**

- |              |   |
|--------------|---|
| 2004-present | Medical Intensive Care Unit. Attending physician 4 to 6 weeks per year, Johns Hopkins.                        |
| 2004-present | Pulmonary Consultation Service. Attending physician four weeks per year, Johns Hopkins.                       |
| 2004-present | Lung Transplantation and Pulmonary Hypertension Service. Attending physician 8 weeks per year, Johns Hopkins. |
| 2004-present | Pulmonary Physiology Service. Attending physician four weeks per year, Johns Hopkins.                         |
| 2005-present | Janeway Firm Faculty. Teaching Attending 4 weeks per year, Johns Hopkins.                                     |

### **CME Instruction**

- |      |   |
|------|---|
| 5/06 | PFT interpretation, Topics/Tumulty Rounds, Johns Hopkins, Baltimore, MD.  |
| 4/06 | Challenging infections among adults with cystic fibrosis. Medical Grand Rounds. Johns Hopkins, Baltimore, MD                    |
| 8/07 | Update in Pulmonary and Critical Care Medicine, Johns Hopkins, Williamsburg VA.   |
| 1/07 | Cough for the Allergist, Allergy Symposium, Bayview Medical Center, Baltimore, MD.  |
| 7/08 | Update in Pulmonary and Critical Care Medicine, Johns Hopkins, Bar Harbor ME.   |
| 2/09 | Hereditary Hemorrhagic Telangiectasia- A Fresh Start to an Old Disease. Medical Grand Rounds. Johns Hopkins, Baltimore, MD.     |
| 7/09 | Update in Pulmonary and Critical Care Medicine, Johns Hopkins, Washington DC.   |
| 1/10 | An update in Cystic Fibrosis, Allergy Lecture Series, Johns Hopkins, Baltimore, MD.   |
| 4/12 | Nutritional Considerations after Lung Transplantation in Cystic Fibrosis. Nutrition Grand Rounds. Johns Hopkins, Baltimore, MD. |
| 9/12 | Hereditary Hemorrhagic Telangiectasia. Medical Grand Rounds. Johns Hopkins Bayview. Baltimore, MD.                              |
| 5/14 | A Curious Case of Hypoxemia, Topics/Tumulty Rounds, Johns Hopkins, Baltimore, MD.   |

9/14 Creating a Common Language in Cystic Fibrosis to Improve Adherence, Lecturer, Med-IQ. [www.med-iq.com/a/796](http://www.med-iq.com/a/796)

### **Workshops/ Seminars**

5/08 Invited Lecturer, Observational Studies, Short Course in Epidemiology. American Thoracic Society, Toronto, ON.

10/09 Symposium Chairperson, Infectious Complications in Cystic Fibrosis. North American Cystic Fibrosis Conference, Minneapolis MN.

10/10 Symposium Chairperson, End Stage Lung Disease in CF: From Lung transplantation to Palliative Care, North American Cystic Fibrosis Conference, Baltimore, MD.

10/10 Invited Lecturer. Rise and Shine Workshop Management of Hemoptysis and Pneumothorax in Cystic Fibrosis. North American Cystic Fibrosis Conference, Baltimore, MD.

### **Mentoring**

#### **Advisees**

2006-2010 Elliott Dasenbrook, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine Johns Hopkins University, currently Assistant Professor of Medicine at Case Western Reserve, Cleveland, OH.

2006-2010 Jeffrey Hoag, MD, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Assistant Professor of Medicine at Drexel University, Philadelphia, PA.

2008-2011 Brad Drummond, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Assistant Professor of Medicine, Johns Hopkins University, Baltimore MD.

2008-2012 Natalie West, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Assistant Professor of Medicine at Johns Hopkins University, Baltimore, MD.

2009-2011 Eric Weiss, MD MPH, Master's of Public Health student at Johns Hopkins Bloomberg School of Public Health, currently Assistant Professor of Surgery (adjunct) at Columbia College of Physicians and Surgeons, New York, NY.

2010-2012 Jeremiah Allen, MD, Resident, Johns Hopkins University, currently Attending Cardiac Surgeon, Kaiser Permanente, San Francisco, CA.

2010-present Andrew Braun, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Instructor of Medicine, Johns Hopkins University, Baltimore, MD.

2011-2013 Timothy George, MD, Resident, Johns Hopkins University, currently Resident Surgeon at Johns Hopkins University, Baltimore, MD.

2011-2014 Arman Kilic, MD, Resident, Johns Hopkins University, currently Resident Surgeon, Johns Hopkins University, Baltimore, MD.

2011-present Mark Jennings, MD, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Instructor of Medicine, Johns Hopkins University, Baltimore, MD.

2012-2016 Allison Lambert, MD MHS, Post-doctoral Fellow, Pulmonary and Critical Care Medicine, Johns Hopkins University, currently Instructor of Medicine, Johns Hopkins University, Baltimore, MD.

2012-2016 George Arnaoutakis, MD, Resident, Johns Hopkins University, currently Cardiac Surgery Fellow, University of Pennsylvania, Philadelphia, PA.

2014-present Joshua Grimm, MD, Resident, Johns Hopkins University, currently Resident Surgeon, Johns Hopkins University, Baltimore, MD.

2014-present Linda Yin, Medical student, Johns Hopkins University, currently a medical student at Johns Hopkins University, Baltimore, MD.

2015-present Todd Crawford, MD, Resident, Johns Hopkins University, currently Resident Surgeon, Johns Hopkins University, Baltimore, MD.

2015-present Trent Magruder, MD, Resident, Johns Hopkins University, currently Resident Surgeon, Johns Hopkins University, Baltimore, MD.

### **Educational Program Building/ Leadership**

2006-present Course Director, Design of Clinical Studies, Johns Hopkins Bloomberg School of Public Health. This is an ongoing course available in the 2<sup>nd</sup> term each year through the Department of Epidemiology in the School of Public Health. It is part of a series of courses known formally together as the Science of

Clinical Investigation series. Together these courses convey the fundamentals of clinical research. In my capacity as director, I am responsible each year for the syllabus, lectures, homework assignments, and follow-up questions which arise during the 12-week class. The course has expanded over the years starting with a class size of about 6-8 to now over 40 per term and now includes physicians, nurses, administrators, and research coordinators.

2012-present Course Director, Distance Education Design of Clinical Studies, Johns Hopkins Bloomberg School of Public Health. This is a fully online version of the above course available through the Office of Distance Education in the 3<sup>rd</sup> term. Lectures, assignments, and quizzes are all available online. Live sessions accompany the online media. This course has also expanded from just a few to over 30 students per session.

**Educational Extramural Funding (Current, Pending, Previous) - None**

## **CLINICAL ACTIVITIES**

### **Certification**

#### Medical

1998	Medical License, Commonwealth of Virginia	0101057430	Inactive
1999	Medical License, District of Columbia	MD31720	Inactive
2004-present	Medical License, Maryland	D0061725	Active

#### Boards

2000	Diplomate, Internal Medicine, American Board of Internal Medicine
2003	Diplomate, Pulmonary Disease, American Board of Internal Medicine
2005	Diplomate, Critical Care Medicine, American Board of Internal Medicine

### **Clinical Responsibilities**

2004-present	Medical Intensive Care Unit. Attending physician 4 to 6 weeks per year, JHH.
2004-present	Pulmonary Consultation Service. Attending physician four weeks per year, JHH.
2004-present	Lung Transplantation and Pulmonary Hypertension Service. Attending physician 8 weeks per year, JHH.
2004-present	Pulmonary Physiology Service. Attending physician four weeks per year, JHH.
2004-present	Attend in the Adult Cystic Fibrosis Clinic. One half day per week
2009-present	Attend in HHT Clinic. One half day per month
2011-present	Attend in the Lung Transplantation Clinic. One half day per week

### **Clinical Program Building/Leadership**

2010-2018	Director, Johns Hopkins Hereditary Hemorrhagic Telangiectasia Center of Excellence. In my capacity, I am responsible for the coordination of multidisciplinary care for the patients with HHT that we care for at Johns Hopkins. Working in partnership with Sally Mitchell, MD, we created the Johns Hopkins HHT Center of Excellence in 2010, one of 17 such centers in the United States. The center now includes over 35 specialists from 15 Hopkins Departments and Divisions and has increased exponentially in size to include over 400 patients and family members. The team at Hopkins now consists of a nurse coordinator as well as specialists from nearly every division and department within the Hopkins system.
2015-present	Associate Program Director, Johns Hopkins Adult Cystic Fibrosis Center. In my capacity, I assist the Program and Center Director in the coordination of care guidelines and the delivery of clinical care in both the inpatient and outpatient settings, assist with coordination of clinical trials, and provide education to medical students, physicians, nurses, respiratory and physical therapists, nutritionists, social workers, patients, and family members regarding the multidisciplinary subspecialty care needed for patients with CF.

**Clinical Extramural Funding (Current, Pending, Previous) - None**

**SYSTEM INNOVATION AND QUALITY IMPROVEMENT ACTIVITIES - None**

## ORGANIZATIONAL ACTIVITIES

### Institutional Administrative Appointments

2003-2005 Educational Committee, Division of Pulmonary and Critical Care Medicine  
 2005-present Faculty Recruitment Committee, Division of Pulmonary and Critical Care  
 2014-present Assistant Director of Outpatient Services, Johns Hopkins Division of Pulmonary and Critical Care Medicine  
 2015-present Associate Program Director, Adult Cystic Fibrosis Center, Johns Hopkins Cystic Fibrosis Center

### Editorial Activities - Not Applicable

### Journal Reviewer

2009-present Chest  
 2009-present Journal of Heart and Lung Transplant  
 2009-present Journal of Cystic Fibrosis  
 2009-present European Respiratory Journal  
 2009-present American Journal of Transplantation

### Advisory Committees, Review Groups/Study Sections

2012-present Member, Cystic Fibrosis Foundation Grant review Committee

### Professional Societies

2004-present Member, American Thoracic Society  
 2004-present Member, American College of Chest Physicians  
 2010-present Member, International Society for Heart and Lung Transplant

### Conference Organizer, Session Chair - Not Applicable

### Consultantships - Not Applicable

## RECOGNITION

### Awards, Honors

1999 Clinical Pearls Student Teaching Appreciation Award  
 1999 The William P. Argy Memorial House Staff Award  
 2000 Alpha Omega Alpha, Georgetown University  
 2003 DC Thoracic Society Annual Conference Award  
 2003 NIH Loan Repayment Program Award for Clinical Research  
 2005 Janeway Firm Faculty  
 2005 CHEST Foundation's Young Investigator Award  
 2005 NIH Loan Repayment Program Award for Clinical Research  
 2010 Fellows Teaching Award, Johns Hopkins

### Invited Talks

#### Local/National/International

2005 Speaker, Medical Grand Rounds. Virginia Hospital Center. "The Care of Adults with Cystic Fibrosis". Arlington, VA  
 2005 Speaker, Pulmonary Grand Rounds. The University of Pittsburgh. "The influence of environmental and genetic factors on outcomes in cystic fibrosis". Pittsburgh, PA.  
 2007 Plenary Speaker, International Society for Heart and Lung Transplant. "The effect of the Lung Allocation Score (LAS) on survival after lung transplantation". San Francisco, CA.  
 2008 Speaker, North American Cystic Fibrosis Conference. "The Impact of the LAS on Outcomes in CF". Orlando, FL.  
 2008 Speaker, Mid Atlantic Thoracic Society Conference. "Adult Cystic Fibrosis". Richmond, VA.  
 2009 Speaker, Hereditary Hemorrhagic Telangiectasia International Scientific Conference. "Quality of Life among Patients with Hereditary Hemorrhagic Telangiectasia". Santander, Spain.  
 2010 Speaker/ Session Chair, Society for General Internal Medicine. "Research During Residency- Striking the Balance at Hopkins". Minneapolis, MN.

- 2010 Speaker/ Session Chair, North American Cystic Fibrosis Conference. "Lung Transplantation and Cystic Fibrosis". Baltimore, MD.
- 2010 Speaker, Pulmonary Grand Rounds. Brown University. "Hereditary Hemorrhagic Telangiectasia". Providence, RI.
- 2010 Speaker, 8<sup>th</sup> International Congress on Lung Transplantation. "Understanding and Dissecting the Lung Allocation Scoring System". Paris, France.
- 2012 Speaker, Medical Grand Rounds. Georgetown University Hospital. "Adult Cystic Fibrosis". Washington, DC.
- 2012 Speaker, 16<sup>th</sup> Annual HHT Patient and Family Day, HHT Foundation, "Understanding Screening for HHT." Orlando, FL.
- 2013 Speaker, American Thoracic Society. "Understanding and Dissecting the Lung Allocation Scoring System". Philadelphia, PA.
- 2013 Speaker, Cystic Fibrosis Conference Mexico. "Outcomes in Adults with Cystic Fibrosis". Mexico City, Mexico.
- 2013 Speaker, Hereditary Hemorrhagic Telangiectasia International Scientific Conference. "Minimal Clinical Important Difference in Epistaxis Severity Score in HHT". Cork, Ireland.
- 2014 Speaker, Medical Grand Rounds. Virginia Hospital Center. "Adult Cystic Fibrosis". Arlington, VA.

#### **OTHER PROFESSIONAL ACCOMPLISHMENTS**

- 2013 Washington Post. When should you start worrying about that lingering cough? Give it time. [http://www.washingtonpost.com/national/health-science/when-should-you-start-worrying-about-that-lingering-cough-give-it-time/2013/12/20/1e615e9c-665d-11e3-ae56-22de072140a2\\_story.html](http://www.washingtonpost.com/national/health-science/when-should-you-start-worrying-about-that-lingering-cough-give-it-time/2013/12/20/1e615e9c-665d-11e3-ae56-22de072140a2_story.html)
- 2013 Hopkins Medicine. For Lung Transplant, Researchers Surprised to Learn Bigger Appears to Be Better. [http://www.hopkinsmedicine.org/news/media/releases/for\\_lung\\_transplant\\_researchers\\_surprised\\_to\\_learn\\_bigger\\_appears\\_to\\_be\\_better\\_](http://www.hopkinsmedicine.org/news/media/releases/for_lung_transplant_researchers_surprised_to_learn_bigger_appears_to_be_better_)
- 2014 Cover photograph entitled "A View of the Dome". Annals of the American Thoracic Society, Volume 11, Issue 5. <http://www.atsjournals.org/toc/annalsats/11/5>
- 2014 Johns Hopkins Health. Calming that cough. [http://www.hopkinsmedicine.org/news/publications/johns\\_hopkins\\_health/fall\\_2014/calming\\_that\\_cough](http://www.hopkinsmedicine.org/news/publications/johns_hopkins_health/fall_2014/calming_that_cough)
- 2015 EurekAlert! Lung transplant patients in the UK fare better than publicly insured Americans. [http://www.eurekalert.org/pub\\_releases/2015-03/jhm-ltp031915.php](http://www.eurekalert.org/pub_releases/2015-03/jhm-ltp031915.php)

# **APPENDIX B**

## APPENDIX B

### List of Literature Review and Materials Considered by Dr. Christian Merlo

1. Abenhaim et al., *Appetite-Suppressant Drugs and the Risk of Primary Pulmonary Hypertension*. (1996) 335(9) N Engl J Med 609
2. Berge et al., *Genital use of talc and risk of ovarian cancer: a meta-analysis*. (2018) 27 Eur J Cancer Prev 248
3. Booth et al., *Risk factors for ovarian cancer: a case-control study*. (1989) 60(4) Br J Cancer. 592
4. Centers for Disease Control & Prevention, *Principles of Epidemiology in Public Health Practice, Third Edition, An Introduction to Applied Epidemiology and Biostatistics, Lesson 1: Introduction to Epidemiology*, <https://www.cdc.gov/opphss/csels/dsepd/ss1978/lesson1/section1.html>
5. Chang & Risch., *Perineal talc exposure and risk of ovarian carcinoma*. (1997) 79(12) Cancer. 2396
6. Chen et al., *Risk factors for epithelial ovarian cancer in Beijing, China*. (1992) 21(1) Int J Epidemiol. 23
7. Cook et al., *Perineal powder exposure and the risk of ovarian cancer*. (1997) 145(5) Am J Epidemiol. 459
8. Cramer & Xu, *Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer*. (1995) 5 Ann Epidemiol. 310
9. Cramer et al., *Ovarian cancer and talc: a case-control study*. (1982) 50(2) Cancer 372
10. Cramer et al., *The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States*. (2016) 27(3) Epidemiology 334
11. Cramer et al., *Genital talc exposure and risk of ovarian cancer*. (1999) 81(3) Int J Cancer. 351
12. Deposition of Anne McTiernan, M.D., Ph.D., Jan. 28, 2019 (MDL No. 2738)
13. Deposition of April Zambelli-Weiner, Ph.D., Jan. 11, 2019 (MDL No. 2738)
14. Deposition of April Zambelli-Weiner, Ph.D., Feb. 7, 2019 (MDL No. 2738)
15. Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738)
16. Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738)
17. Deposition of Jack Siemiatycki, Jan. 31, 2019 (MDL No. 2738)
18. Deposition of Rebecca Smith-Bindman, M.D., Feb. 7, 2019 (MDL No. 2738)
19. Deposition of Rebecca Smith-Bindman, M.D., Feb. 8, 2019 (MDL No. 2738)
20. Deposition of Patricia Moorman, M.S.P.H., Ph.D., Jan. 25, 2019 (MDL No. 2738)
21. Deposition of Sonal Singh, M.D., M.P.H., Jan. 16, 2019 (MDL No. 2738)
22. Doll & Hill, *The mortality of doctors in relation to their smoking habits*. (1954) 328 (7455) BMJ 1529
23. Expert Report of Anne McTiernan, M.D., Ph.D., Nov. 16, 2018 (MDL No. 2738)
24. Expert Report of April Zambelli-Weiner, Ph.D., M.P.H., Nov. 16, 2018 (MDL No. 2738)
25. Expert Report of Ghassan Saed, Ph.D., Nov. 16, 2018 (MDL No. 2738)
26. Expert Report of Jack Siemiatycki, M.Sc., Ph.D., Nov. 16, 2018 (MDL No. 2738)
27. Expert Report of Patricia Moorman, M.S.P.H., Ph.D., Nov. 16, 2018 (MDL No. 2738)
28. Expert Report of Rebecca Smith-Bindman, M.D., Nov. 15, 2019 (MDL No. 2738)
29. Expert Report of Sonal Singh, M.D., M.P.H., Nov. 16, 2018 (MDL No. 2738)

30. Gates et al., *Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype*. (2010) 171 Am. J. Epidemiology 45
31. Gates et al., *Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer*. (2008) 17(9) Cancer Epidemiol Biomarkers 2436
32. Gertig et al., *Prospective Study of Talc Use and Ovarian Cancer*. (2000) 92 J. Nat. Cancer Inst. 249
33. Godard et al., *Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study*. (1998) 179(2) Am J Obstet Gynecol. 403
34. Gonzalez et al., *Douching, Talc Use, and Risk of Ovarian Cancer*. (2016) 27 Epidemiology 797
35. Green A, Purdie D, Bain C, et al., *Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group*. (1997) 71(6) Int J Cancer. 948
36. Grimes & Schultz, *Bias and causal associations in observational research*. (2002) 259(9302) Lancet 248
37. Gross & Berg, *A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer*. (1995) 5(2) J Expo Anal Environ Epidemiol. 181
38. Harlow & Weiss, *A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc*. (1989) 130(2) Am J Epidemiol. 390
39. Harlow et al., *Perineal exposure to talc and ovarian cancer risk*. (1992) 80(1) Obstet Gynecol. 19
40. Hartge & Stewart., *Occupation and ovarian cancer: a case-control study in the Washington, DC, metropolitan area, 1978-1981*. (1994) 36(8) J Occup Med. 924
41. Hartge et al., *Talc and Ovarian Cancer*, (1983) 250 J. Am. Med. Ass'n 1844
42. Hill, *Environment and disease: association or causation?* (1965) 58 Proc Royal Soc Med. 295
43. Houghton et al., *Perineal Powder Use and Risk of Ovarian Cancer*. (2014) 106(9) J Nat. Cancer Inst
44. Huncharek et al., *Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-analysis of 11,933 Subjects from Sixteen Observational Studies*. (2003) 23 Anticancer Res. 1955
45. Huncharek et al., *Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies*. (2007) 18 Eur J Cancer Prev 422
46. Infante-Rivard, *Hospital or Population Controls for Case-Control Studies of Sever Childhood Diseases?* (2003) 157(2) Am J Epidemiol 176
47. Jordan et al., *Risk factors for benign, borderline and invasive mucinous ovarian tumors: Epidemiological evidence of a neoplastic continuum?* (2007) 107 Gynecol. Oncol. 223
48. Jordan et al., *Risk factors for benign serous and mucinous epithelial ovarian tumors*. (2007) 109(3) Obstet Gynecol. 647
49. Kurta et al., *Use of Fertility Drugs and Risk of Ovarian Cancer: Results from a U.S.-Based Case-Control Study*. (2012) 21(8) Cancer Epidemiol Biomarkers Prev. 1282
50. Langseth et al., *Perineal use of talc and risk of ovarian cancer*. (2008) 62 J Epidemiol Community Health 358
51. Malmberg et al., *Serous tubal intraepithelial carcinoma, chronic fallopian tube injury, and serous carcinoma development*. (2016) 468(6) Virchows Arch. 707-13
52. Merritt et al., *Talcum Powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer*. (2008) 122 Int'l J. Cancer 170

53. Mills et al., *Perineal Talc Exposure and Epithelial Ovarian Cancer Risk in the Central Valley of California*. (2004) 112 Int'l J. Cancer 458
54. Moorman et al., *Ovarian Cancer Risk Factors in African-American and White Women*. (2009) 170(5) Am J Epidemiol 598
55. Narod, *Talc and ovarian cancer*. (2016) 141 Gynecol. Oncol. 410
56. Nat. Cancer Inst., *Cancer Stat Facts: Ovarian Cancer*, <https://seer.cancer.gov/statfacts/html/ovary.html>
57. Nat. Cancer Inst., *Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ) – Health Professional Version*, [https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#link/\\_220\\_toc](https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq#link/_220_toc) (last updated Jan. 4, 2019)
58. Nat. Health & Medical Res. Council, *NHMRC Levels of Evidence and Grades for Recommendations for Developers of Clinical Practice Guidelines* (2009)
59. Ness et al., *Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer*. (2000) 11(2) Epidemiology 111
60. Oleckno, *Epidemiology: Concepts and Methods*. (2008)
61. Penninkilampi and Eslick, *Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis*. (2018) 29(1) Epidemiology 41
62. Pike et al., *Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study*. (2004) 82(1) Fertil Steril. 186
63. Purdie et al., *Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study*. Survey of Women's Health Study Group. (1995) 62(6) Int J Cancer. 678
64. Rosenblatt et al., *Genital powder exposure and the risk of epithelial ovarian cancer*. (2011) 22 Cancer Causes Control 737
65. Rosenblatt et al., *Mineral Fiber Exposure and the Development of Ovarian Cancer*, (1992) 45 Gynecologic Oncology 20
66. Rosenblatt et al., *Characteristics of women who use perineal powders*. (1998) 92(5) Obstet Gynecol 753
67. Schildkraut et al., *Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)*. (2016) 25(10) Cancer Epidemiol Biomarkers Prev. 1411
68. Schlesselman, *Case-control studies: design, conduct, analysis* (1982)
69. Schultz & Grimes, *Case-control studies: research in reverse*. (2002) 359(9304) Lancet 431
70. Shushan et al., *Human menopausal gonadotropin and the risk of epithelial ovarian cancer\**. (1996) 65(1) Fertil Steril. 13
71. Terry et al., *Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls*. (2013) 6(8) Cancer Prev Res 811
72. The Scandinavian Simvastatin Survival Study Group. *Design and baseline results of the Scandinavian Simvastatin Survival Study of patients with stable angina and/or previous myocardial infarction*. (1993) 71 Am J Cardiol 393
73. Tzonou et al., *Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer*. (1993) 55(3) Int J Cancer. 408
74. Vavken & Dorotka, *A Systematic Review of Conflicting Meta-Analyses in Orthopaedic Surgery*. (2009) 467(10) Clin Orthop Relat Res. 2723

75. Vetter & Mascha, *Bias, Confounding, and Interaction: Lions and Tigers, and Bears, Oh My!*, (2017) 125(3) *Anesth Analg* 1042
76. Wang et al., *Statistics in Medicine – Reporting of Subgroup Analyses in Clinical Trials*. (2007) 357(21) *N Engl J Med* 2189
77. Whittemore et. al., *Personal And Environmental Characteristics Related To Epithelial Ovarian Cancer*, (1988) 128 *Am J. Epidemiol* 1228
78. Wong et al. *Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study*. (1999) 93 *Obstet Gynecol* 372
79. Wu et al., *African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates*. (2015) 24(7) *Cancer Epidemiol Biomarkers Prev.* 1094
80. Wu et al., *Markers of inflammation and risk of ovarian cancer in Los Angeles County*. (2009) 124 *Int'l J. Cancer* 1409
81. Wynder et al., *Radford Conference Report: Weak associations in epidemiology and their interpretation (3rd ed.)*. (1982) 11 *Prev. Med*

# APPENDIX C

72262  
Fed. R. Civ. P. 26(a)(2)(B)(v) Disclosure for Christian Merlo, M.D., M.P.H.

Year	Parties	State	Caption
2015	Blevins v. Pyron	Missouri	Blevins v. Pyron Lawrence County Circuit Court 14LW-CC00108
2015	Grove v. UMMS	Maryland	Grove v. UMMS USDC Maryland 12-cv-2950
2015	Dutton v. UMMS	Maryland	Dutton v. UMMS Baltimore City Circuit Court 24-C-14-003848
2015	Hawkins v. Mercy Kansas	Missouri	Hawkins v. Mercy Kansas St. Louis City Circuit Court 1422-CC09810
2015	Whitehead v. CVS	Florida	Whitehead v. CVS Miami-Dade County Circuit Court 14-25980CA01
2016	Evans v. Livingston Health Care	Montana	Evans v. Livingston Health Care Gallatin County District Court DV-11-990B
2016	Moore v. Mercy	Maryland	Moore v. Mercy Baltimore City Circuit Court 24-C-16-004483
2016	Quintanilla v. Narayanan	Maryland	Quintanilla v Narayanan Montgomery County Circuit Court 397252V
2017	Burns v. Bowser	Virginia	Burns v. Bowser Virginia 13th Judicial Circuit CL14005484-00
2017	Monroe v. Franklin Square	Maryland	Monroe v. Franklin Square Baltimore County Circuit Court 03-C-16-001886
2017	Weisman v. Maryland General	Maryland	Weisman v. Maryland General Baltimore City Circuit Court 24-C-16-004199
2017	Almquist v. Kinsey	Maryland	Almquist v. Kinsey USDC Maryland 1:15cv292
2017	Sullivan v. Holy Cross	Maryland	Sullivan v. Holy Cross Montgomery County Circuit Court 423516v
2018	Flores v. Kaiser	Maryland	Flores v. Kaiser Montgomery County Circuit Court 427661v
2018	Hamlin-Lewis v. Guckes	Maryland	Hamlin-Lewis v. Guckes USDC Maryland 1:16cv3357
2018	Hirschenson v. Cleveland Clinic	Florida	Hirschenson v. Cleveland Clinic Broward County Circuit Court CACE13001180
2018	Knoerlein v. Express Primary Care	Maryland	Knoerlein v. Express Primary Care Baltimore County Circuit Court 03-C-17-001137
2018	McRae v. Dimensions Health	Maryland	McRae v. Dimensions Health Prince George's County Circuit Court CAL1702184
2018	Fluoroquinolone Liability Litigation	New Jersey	
2019	Jones v. Agrawal	Maryland	Jones vs Bon Secours Hospital Baltimore, Inc, et al ("Jones v. Agrawal") Baltimore County Circuit Court 24C18000398

# Exhibit 149

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

**IN RE: JOHNSON & JOHNSON TALCUM  
POWDER PRODUCTS MARKETING, SALES  
PRACTICES AND PRODUCTS LIABILITY  
LITIGATION**

**MDL NO. 16-2738 (FLW) (LHG)**

***THIS DOCUMENT RELATES TO ALL CASES***

**EXPERT REPORT OF GREGORY DIETTE, MD, MHS  
FOR GENERAL CAUSATION *DAUBERT* HEARING**

Date: February 25, 2019

A handwritten signature in blue ink, appearing to read 'G Diette', is positioned above a horizontal line.

Gregory Diette, M.D., M.H.S.

## **I. SCOPE OF REPORT**

I was retained by Johnson & Johnson and Johnson & Johnson Consumer Inc. to review the epidemiological literature regarding the hypothesized connection between talc or asbestos in talc and the development of ovarian cancer.

## **II. MY QUALIFICATIONS**

I am a professor of medicine at the Johns Hopkins University School of Medicine. I hold joint appointments in the Departments of Environmental Health Sciences and Epidemiology in the Johns Hopkins Bloomberg School of Public Health.

I received my M.D. from the Temple University School of Medicine. I completed my residency at the Hospital of the University of Pennsylvania and performed a fellowship in pulmonary and critical care medicine at Johns Hopkins. I received my M.H.S. in Epidemiology and Clinical Epidemiology from the Johns Hopkins Bloomberg School of Public Health. Currently, I am an attending Physician at the Johns Hopkins Hospital and the Johns Hopkins Bayview Medical Center, practicing both inpatient and outpatient care.

My areas of clinical expertise include internal medicine, pulmonary medicine and critical care medicine. My areas of research include environmental impacts on lung disease and epidemiology of chronic diseases. I have published more than 200 studies in peer-reviewed journals on a variety of medical and scientific subjects, including the epidemiological study of disease causation, disease risk factors and gene expression, as well as the health effects of environmental pollutants. In addition, I am a peer reviewer for a number of journals. I have also repeatedly lectured and instructed on advanced research methods in epidemiology.

I currently hold multiple positions related to teaching and clinical research. I am an attending physician at Johns Hopkins and a member of the American Thoracic Society, where I served on the Board of Directors and have participated in a number of its teaching programs, including the Methods in Epidemiologic, Clinical and Operations Research program. I also previously served as the Director of Clinical Research in the Division of Pulmonary and Critical Care Medicine for almost 14 years.

Additional information pertaining to my background and qualifications can be ascertained from my curriculum vitae, which is attached to this report, together with other required disclosures. I am being compensated at a rate of \$485 per hour for my work on this case and \$600 per hour for testimony.

## **III. SUMMARY OF OPINIONS**

The body of relevant epidemiological evidence does not support a causal connection between perineal use of talcum powder products (whatever constituents those products may contain in addition to talc) and ovarian cancer. As fully set forth below:

1. The epidemiological literature shows a non-existent association or, at most, a small association between perineal talc use and ovarian cancer that constitutes only weak epidemiological evidence. Because any purported association demonstrated in the literature is weak, it may well be attributed to factors such as confounding, bias or chance.
2. Studies have not consistently shown an association. The prospective epidemiological studies (cohort studies) do not show a statistically significant association; the hospital-based case-control studies do not show a statistically significant association; and only a subset of the population-based case-control studies show a statistically significant association. If consistency could be drawn from these inconsistent results, it would be a consistency of null results because case-control studies, which are more easily subject to certain biases and confounding factors, are not the best evidence for proving causation.
3. Evidence of a dose-response relationship is lacking. None of the cohort studies reveals a dose-response relationship, and only a handful of case-control studies, including those analyzing “cumulative” talc use, have purported to find one. Moreover, study authors and plaintiffs’ experts all agree that there are major challenges to interpreting the study findings on dose-response because there can be no assurance that any estimates of talc use are accurate or valid. Indeed, there is not a single epidemiologic study of ovarian cancer and talcum powder that has used, or purports to have used, a validated measure of talcum powder use. Without a validated measure of talcum powder use, it is impossible to correctly determine whether or not an exposure occurred or the quantity of purported exposure, casting considerable doubt on any purported causative relationship between perineal talcum powder use and ovarian cancer.
4. The theories as to how talc or asbestos would reach the ovaries have not been validated, and the scientific community has repeatedly expressed the opinion that the potential mechanism by which talcum powder is associated with ovarian cancer remains speculative.
5. Additional Bradford Hill factors – temporality, coherence of the association and analogy – are not satisfied based on the available epidemiologic evidence and do not support the allegation that talcum powder use can cause ovarian cancer.
6. To the extent plaintiffs’ experts opine that asbestos is an accessory mineral present in cosmetic talc that causes ovarian cancer, this theory would not alter the analysis because the existing epidemiological literature regarding perineal talc use would necessarily account for the presence of any asbestos in the products used in those studies. Plaintiffs’ experts’ asbestos-based theories are also problematic due to the lack of a plausible mechanism by which asbestos could reach the ovaries and a lack of any reliable epidemiology supporting such a causal connection.

#### **IV. APPROACH**

##### **A. Bradford Hill Framework**

Epidemiologists and other scientists are often tasked with determining whether or not an exposure can cause an illness or condition. After an association has been demonstrated, criteria articulated by Austin Bradford Hill in a lecture in 1965 are often employed. These Bradford Hill considerations, or criteria, are considered the gold standard for assessing causation based on observed associations. The nine considerations are: consistency, strength of association, specificity, dose-response relationship, temporality, biologic plausibility, coherence of the association, analogy and experimentation.<sup>1</sup> In applying these criteria, an epidemiologist should consider all available evidence, which can be assessed and graded according to its sufficiency (or lack thereof) to establish a causal link. Evidence typically comes from research studies that involve humans, but it can also include well-designed studies of animals or in vitro systems (toxicological and experimental) to provide supportive evidence, especially for plausibility.

Another useful factor for assessing causation includes consideration of non-causal explanations for the results of individual studies.<sup>2</sup> As explained further below, these other explanations can come from bias, confounding and chance. For example, drinking coffee might be correlated with a higher risk of lung cancer, but the cause of the additional cases of lung cancer among individuals who drink coffee would be smoking cigarettes. In this example, the obvious confounding factor is that individuals who drink coffee are more likely to smoke. But confounding factors are not always identifiable, even after extended study, and these and other factors can consistently drive statistical associations that are not causal in nature. Such limitations can be quite important, as they can lead to risk estimates that are falsely higher or lower than actual risk, and they can even lead to conclusions that an exposure causes a disease when it does not, and vice versa.

##### **B. Methodology**

I was asked to assess whether perineal exposure to talcum powder causes ovarian cancer. Based on my extensive qualifications and experience, review of the available studies and data and assessment of the Bradford Hill factors, I conclude that the observations and evidence to date are insufficient to find a causal relationship between perineal exposure to talcum powder and ovarian cancer.

My opinions are based on a review of the epidemiology literature relevant to the evaluation of the association between perineal talcum powder use and ovarian cancer. In my review, I considered case-control studies, prospective cohort studies and meta-analyses. I did not consider randomized trial data, since I am not aware of any such data reporting on the presence

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<sup>1</sup> Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med. 1965; 58(5):295-300 ("Hill 1965").

<sup>2</sup> Elwood JM. Causal Relationships in Medicine: A Practical System for Critical Appraisal. Oxford: 1988, 163-182.

or absence of an association between of talcum powder and ovarian cancer. Because the accuracy of the findings of case-control and cohort studies can be influenced by bias and confounders, I carefully considered whether there was any indication that these sorts of errors affected the results.

In evaluating the epidemiologic data and other scientific evidence under the Bradford Hill framework, I primarily focus on whether the criteria of strength of association, consistency of the association, biologic gradient (or dose response) and biologic plausibility have been met. Although it is not essential to address every factor under the Bradford Hill framework, as plaintiffs' experts acknowledge,<sup>3</sup> I also address specificity, temporality, coherence of the association, experiment and analogy.

Lastly, I reviewed several of the reports submitted by plaintiffs' experts and their depositions. A number of these experts claim to have analyzed the Bradford Hill criteria and to have concluded through these analyses that perineal talc use causes ovarian cancer. I assess and address several of plaintiffs' experts' methods and analyses in this regard.

## **V. STUDY DESIGNS**

Epidemiologists recognize that there is a hierarchy of evidence with respect to human studies. Clinical trials are often considered the strongest type of evidence, followed by observational studies (cohort and case-control). The lowest quality of evidence comes from case reports, case series and descriptive studies.<sup>4</sup>

There are two main types of epidemiological studies at issue here: prospective cohort studies and case-control studies.

Prospective cohort studies consist of identifying a large group of healthy individuals who differ in the key areas being observed and following them forward in time. Based on the data collected, it is determined how the factors of interest, e.g., exposure to talcum powder, are associated with a certain outcome or disease. Cohort studies are widely regarded as more reliable than retrospective case-control studies because they are not susceptible to recall bias, which is the propensity of study subjects with the disease that is being studied to inaccurately report their exposure to the agent at issue, a phenomenon that can generate inflated risk estimates.<sup>5</sup> Cohort studies generally avoid this pitfall because they are prospective rather than retrospective.<sup>6</sup> Due to the ability of cohort studies to assess exposure at baseline instead of relying solely on recall, they can be better suited to detect risks from exposure to an agent.

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<sup>3</sup> Smith-Bindman Rep. at 36; Singh Rep. at 62.

<sup>4</sup> Elwood at 174-175.

<sup>5</sup> Gertig DM, Hunter DJ, Cramer DW, et al. Prospective Study of Talc Use and Ovarian Cancer. *J Natl Cancer Inst.* 2000; 92(3): 249-252, 252 ("Gertig 2000"); Langseth H, Hankinson SE, Siemiatycki J, Weiderpass E. Perineal Use of Talc and Risk of Ovarian Cancer. *J Epidemiol Community Health.* 2008; 62(4):358-360, 358 ("Langseth 2008"). *See generally* Leon Gordis. *Epidemiology.* 5th ed. Philadelphia, PA: 2014.

<sup>6</sup> Although there are also retrospective cohort studies, those are not at issue here, because the cohort studies involving cosmetic talc use are prospective in design.

In case-control studies, individuals with the disease of interest (cases) and those without the disease of interest (controls) are first identified. These two groups are then compared to assess any differences between them regarding a specified exposure. Case-control studies can be further broken down into population-based and hospital-based studies. Hospital-based studies draw their control population from patients who are hospitalized with conditions other than the one under study. Population-based studies draw study participants from the general population.

## **VI. REVIEW OF EPIDEMIOLOGY DATA**

In forming my opinions, I employed search tools, including Medline and Google Scholar, to identify studies that examined the association of perineal talcum powder use and ovarian cancer. I also reviewed the reference lists of individual studies and the meta-analyses to assemble a complete list of studies. Specifically, I first located and reviewed the relevant cohort studies, meta-analyses and case-control epidemiologic studies. I then reviewed how other medical experts or other professional organizations interpreted those studies. My reliance list, which is attached to this report, is comprised of all studies located and assessed specifically for this case. In total, I identified and reviewed 32 case-control studies and three prospective cohort studies published since 1982 that pertain to perineal talc use and ovarian cancer.

It is my understanding that plaintiffs are asserting in this litigation that talc products contain asbestos. The epidemiological literature concerning talc products and ovarian cancer generally has not attempted to investigate the question whether asbestos is present in talc as an accessory mineral. Nevertheless, if talc products have generally contained asbestos, the epidemiological literature would reflect the risks of asbestos in talc.

### **A. Strength Of Association Is Weak.**

The first Bradford Hill criterion, strength of the association, refers to the magnitude of the risk of developing a given outcome in the presence of a measured risk factor. In the studies discussed in this report, risk is reported in various ways – as a relative risk (“RR”), odds ratio (“OR”), or hazard ratio (“HR”) – typically with a confidence interval (“CI”). A relative risk “of an event is the likelihood of its occurrence after exposure to a risk variable” – here, talcum powder or asbestos – “as compared with the likelihood of its occurrence in a control or reference group.”<sup>7</sup> An odds ratio is “a comparison of the odds of an event after exposure to a risk factor with the odds of that event in a control or reference situation.”<sup>8</sup> A hazard ratio is a type of relative risk that measures “how often a particular event happens in one group compared to how often it happens in another group, over time.”<sup>9</sup> In each case, the risk is expressed as a number for which 1 is the denominator, so that a relative risk of 1.3, for example, would mean that the outcome of interest occurred 1.3 times as often in the exposed group as compared to the control

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<sup>7</sup> Andrade C. Understanding Relative Risk, Odds Ratio, and Related Terms. J Clin Psychiatry. 2015; 76(7):e857-861.

<sup>8</sup> *Id.*

<sup>9</sup> National Cancer Inst., NCI Dictionary of Cancer Terms, “hazard ratio,” <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/hazard-ratio>.

group – a 30% greater incidence. A relative risk of 1.0, by contrast, would mean there was no difference. In each case, a confidence interval can be calculated to determine statistical significance – in essence, whether the difference between the exposed and unexposed groups is likely to persist if the same study were repeated. When a confidence interval contains 1.0, the result is deemed not to be statistically significant because the possibility that there is no real association is within the expected range of results. It is typical to calculate a 95% confidence interval, expressed in this report as “95% CI,” meaning that if the study were repeated, the results would be expected to fall within the confidence interval 95% of the time.

While there is no absolute cutoff to define a large versus a small relative risk, Hill provided examples of large risks, including the 200 times risk of scrotal cancer in chimney sweeps, an estimate of 9-10 times risk of lung cancer in smokers and 20-30 times risk of lung cancer in heavy smokers. As an example of a low risk, Dr. Hill used death from coronary thrombosis in smokers, which he described as “no more than twice, probably less” than the death rate in non-smokers. Dr. Hill further explained:

“[T]hough there is good evidence to support causation it is surely much easier in this case to think of some features of life that may go hand in hand with smoking—features that might conceivably be the real underlying cause or, at the least, an important contributor, whether it be lack of exercise, nature of diet or other factors. But to explain the pronounced excess in cancer of the lung in any other environmental terms requires some feature of life so intimately linked with cigarette smoking and with the amount of smoking that such a feature should be easily detectable.”<sup>10</sup>

What this passage from Hill means is that low observed risks are more likely to be non-causal than are high risks, because the effects of distorting factors (such as confounders and bias) have a greater chance of being the true explanation for the observations. Because very small risks are obviously highly susceptible to distorting effects in observational studies, further evidence is required to demonstrate that the purported association did not arise from bias, confounding or chance alone. Plaintiffs’ experts express opinions about risks articulated as approximately a 1.2-1.3 odds ratio.<sup>11</sup> This is considered a weak association by the scientific community, as some of plaintiffs’ experts acknowledge.<sup>12</sup> To the extent other plaintiffs’ experts dispute this point (most notably Dr. Moorman, who attempted to argue that straightforward adjectives like “weak,” “modest” or “strong” do not have “clear definitions”), their position is simply not credible, and even Dr. Moorman acknowledges that 1.2-1.3 is “weaker” than well-established large associations such as smoking/lung cancer.<sup>13</sup> While the size of the risk does not, in itself, determine causation, this purported low risk estimate is not strong evidence of

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<sup>10</sup> Hill 1965.

<sup>11</sup> Moorman Rep. at 17.

<sup>12</sup> Singh Dep. 140:19-25 (agreeing that scientific literature does not consider 1.3 a strong association).

<sup>13</sup> Moorman Dep. 246:24-250:16; *id.* 287:14-289:3 (refusing to define a “weak association” but acknowledging that epidemiology textbooks would not agree that it cannot be defined); *see also id.* 145:4-17 (agreeing that the medical community accepts smoking as a cause of lung cancer but questioning the definition of “medical community” when asked the same about talc and ovarian cancer).

causation. As plaintiffs' expert, Dr. Siemiatycki, wrote in a 1988 article, "[s]mall excess relative risks, even if they are statistically significant, are often interpreted with great caution, if not skepticism."<sup>14</sup>

1. Results Of Cohort Studies, Case-Control Studies And Meta-Analyses And Pooled Studies

As fully set forth in the next sections, the prospective epidemiological studies (cohort studies) do not show a statistically significant association between genital talc use and ovarian cancer, while a subset of the population-based case-control studies do show weak statistically significant associations.

a. Results of Cohort Studies

The most recent cohort study, referred to by many as the "Sister Study," enrolled 50,884 women in the U.S. and Puerto Rico beginning in 2003, who had a sister diagnosed with breast cancer, and followed 41,654 of those women for a median 6.5 years.<sup>15</sup> The study identified 154 cases of ovarian cancer and found no association between the use of talc and ovarian cancer – in fact, there was an inverse association that was not statistically significant (HR 0.73 (95% CI: 0.44-1.2)).<sup>16</sup> Of note, this study separately found an association between douching and ovarian cancer, suggesting that douching (which sometimes accompanies perineal talc use) may be a confounding variable that has not sufficiently been accounted for in past studies.<sup>17</sup>

A prior cohort study known as the Women's Health Initiative Study followed 61,576 women for a mean of 12.4 years.<sup>18</sup> The study showed no increased risk of ovarian cancer from genital use of talc (HR 1.12 (95% CI: 0.92-1.36)), no increased risk of ovarian cancer from genital talc use for 10 or more years (HR 0.98 (95% CI: 0.75-1.29)) or 20 or more years (HR 1.10 (95% CI: 0.82-1.48)), and no increased risk of ovarian cancer with talc use on sanitary napkins (HR 0.95 (95% CI: 0.76-1.20)) or contraceptive diaphragms (HR 0.92 (95% CI: 0.68-1.23)).<sup>19</sup> The result for combined powder use was a statistically non-significant hazard ratio (HR 1.06 (95% CI: 0.87-1.28)) and an even lower statistically non-significant hazard ratio for combined use for more than ten years (HR 1.02 (95% CI: 0.80-1.30)).<sup>20</sup> The authors concluded

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<sup>14</sup> Siemiatycki Dep. 328:22-329:2.

<sup>15</sup> Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR. Douching, Talc Use, and Risk of Ovarian Cancer. *Epidemiology*. 2016; 27(6): 797–802. ("Gonzalez 2016").

<sup>16</sup> *Id.* at 800-02.

<sup>17</sup> *Id.* at 800.

<sup>18</sup> Houghton SC, Reeves KW, Hankinson SE, et al. Perineal Powder Use and Risk of Ovarian Cancer. *J Natl Cancer Inst*. 2014; 106(9): dju208. ("Houghton 2014").

<sup>19</sup> *Id.*

<sup>20</sup> *Id.*

that “perineal powder use does not appear to influence ovarian cancer risk.”<sup>21</sup>

The results of an additional cohort study were published in 2000<sup>22</sup> and updated in another publication ten years later.<sup>23</sup> These reports looked at talc use within the Nurses’ Health Study (“NHS”), which was a prospective cohort of 121,700 registered nurses in the United States and was established in 1976.<sup>24</sup> The Gertig analysis showed no statistically significant association between perineal talc use (RR 1.09 (95% CI: 0.86-1.37)), use of talc on sanitary napkins (RR 0.89 (95% CI: 0.61-1.28)) and for both uses combined (RR 0.90 (95% CI: 0.59-1.37)).<sup>25</sup> It further showed no statistically significant association for various different frequencies of use and no indication that risk increased with more frequent use: less than one per week (RR 1.14 (95% CI: 0.81-1.59)); 1-6 uses per week (RR 0.99 (95% CI: 0.67-1.46)); daily use (RR 1.12 (95% CI: 0.82-1.55)).<sup>26</sup> When examining the results by histology, the authors observed a weak statistically significant association for serous invasive (RR 1.40 (95% CI: 1.02-1.91)) but no other types of ovarian cancer.<sup>27</sup> They noted that perineal talc use “may modestly increase the risk of invasive serous ovarian cancers” but not for “all serous cancers (including borderline cancers), endometrioid cancers, or mucinous cancers,” and concluded overall that their “results provide little support for any substantial association between perineal talc use and ovarian cancer risk.”<sup>28</sup>

The 2010 Gates report, which followed up on the Nurses’ Health cohort ten years later, found no statistically significant elevations in risk for talc use for all epithelial ovarian cancers (RR 1.06 (95% CI: 0.89-1.28)), serous invasive ovarian cancers (RR 1.06 (95% CI: 0.84-1.35)), endometrioid ovarian cancers (RR 1.06 (95% CI: 0.66-1.69)), or mucinous ovarian cancers (RR 1.50 (95% CI: 0.84-2.66)).<sup>29</sup> The authors concluded that their results for talc exposure “generally are consistent with the existing literature,” i.e., consistent with generally null and/or weakly associated results.<sup>30</sup> It is notable too, that with further passage of time, there was no longer an increased association for the serous invasive type of ovarian cancer.

Plaintiffs’ experts’ argument that the Gates report should be disregarded because the participants in the Nurses’ Health Study were only asked about talcum powder use once is

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<sup>21</sup> *Id.*

<sup>22</sup> Gertig 2000.

<sup>23</sup> Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype. *Am J Epidemiol.* 2010; 171(1):45-53, 50 (“Gates 2010”).

<sup>24</sup> Gertig 2000.

<sup>25</sup> *Id.* at 251.

<sup>26</sup> *Id.*

<sup>27</sup> *Id.*

<sup>28</sup> *Id.* at 250-51.

<sup>29</sup> Gates 2010 at 50.

<sup>30</sup> *Id.* at 51. While the 2010 NHS updated the number of women studied, the new participants were not asked about talc, which the authors acknowledged was a “weakness[]” in the study. *Id.* at 52.

unfounded.<sup>31</sup> Ten additional years of follow-up is valuable data regardless of whether further questioning regarding talc use took place. Moreover, as other studies and plaintiffs' experts themselves have admitted, for women who are ever-users of perineal talcum powder, the mean duration of use is greater than 20 years<sup>32</sup> and the vast majority of women who use talcum powder initiate use before age 36.<sup>33</sup> That means that, even though the participants were only asked about their talcum powder use once, the data collected on perineal talcum powder application would have likely reflected chronic, habitual use. For similar reasons, recent meta-analyses by Penninkilampi (relied on heavily by plaintiffs' experts)<sup>34</sup> and Taher<sup>35</sup> (discussed further below) are of questionable value in light of their omission of the findings reported by Gates, which are derived from a cohort study that found no statistically significant elevations in risk for talc users with respect to epithelial ovarian cancers, serous invasive ovarian cancers, endometrioid ovarian cancers or mucinous ovarian cancers.

Dr. McTiernan's argument that cohort studies are limited because they were "designed to study a large number of outcomes and a wide variety of exposures" in addition to talc and ovarian cancer<sup>36</sup> is also wrong. The fact that cohort studies are able to study many variables and outcomes is an illustration of what is valuable and can be achieved with cohort studies. I know of no epidemiologists who believe that the results of all cohort studies should be discounted due to this common design trait; indeed, such a view would conflict with the generally accepted principle that cohort studies can produce a higher level of evidence than case-control studies. Moreover, the typical concern when studies include multiple variables is that they might report false positive associations for particular variables, and no plaintiffs' expert argues that the talc results in cohort studies are false positives (although that argument could be applied to the single positive finding from the Gertig study). Dr. McTiernan relatedly argues that the cohort studies were not "able to accurately measure dose of exposure," but this is equally true of case-control studies, as discussed herein.<sup>37</sup>

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<sup>31</sup> Singh Dep. 164:16-23; Moorman Dep. 190:4-24; McTiernan Dep. 224:3-7; Smith-Bindman Rep. at 20.

<sup>32</sup> Wu AH, Pearce CL, Tseng CC, Pike MC. African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. *Cancer Epidemiol Biomarkers Prev.* 2015; 24(7):1094-100 ("Wu 2015").

<sup>33</sup> Singh Dep. 165:2-8; Gates MA, Tworoger SS, Terry KL, et al. Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 2008; 17(9):2436-2444 ("Gates 2008").

<sup>34</sup> Penninkilampi R, Eslick GD. Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. *Epidemiology.* 2018; 29(1):41-49, 44 ("Penninkilampi 2018"); Smith-Bindman Rep. at 27 ("Penninkilampi provides a comprehensive and high quality review"); McTiernan Rep. at 49 ("[T]he results of this 2018 meta-analysis give strong support for an association between perineal talcum powder product use and risk for ovarian cancer.").

<sup>35</sup> Taher MK, Farhat N, Karyakina NA, et al. Systematic Review and Meta-Analysis of the Association Between Perineal Use of Talc and Risk of Ovarian Cancer (2018) (unpublished manuscript) ("Taher 2018").

<sup>36</sup> McTiernan Rep. at 46.

<sup>37</sup> *Id.*

Plaintiffs' experts also criticize cohort studies for having short follow-up and therefore supposedly not considering the latency period for ovarian cancer.<sup>38</sup> In light of the data noted above about mean initiation and duration of talc use, it is reasonable to assume that the date on which study participants were asked about their talcum powder use was not the date of first use and thus not the date that a true latency period would have begun. Moreover, the Women's Health Initiative Study asked about talcum powder use for 20-plus years and found no statistically significant increased risk in ovarian cancer after following those women for 12.4 years (meaning at least 32.4 years of latency were factored in),<sup>39</sup> and the Sister Study enrolled women between the ages of 35-74 and followed up after 6 years.<sup>40</sup> Therefore, it is clear in the case of the WHI study, and quite likely in the case of the Sister Study, that substantial numbers of cohort study participants were using talcum powder for decades, long enough to put any serious concerns about latency to rest.

Any criticism of the studies that rests on the idea of a latency period is highly speculative anyway. For the reasons set out in this report, science has not even established a causal relationship between talc and ovarian cancer of any sort; far less has it established a latency effect or the duration of any such effect. There is simply no scientific basis for the suggestion of a number of plaintiffs' experts that it takes 20 years for some unspecified degree of perineal talc exposure to cause ovarian cancer.

Finally, plaintiffs' experts' criticisms of cohort studies are collectively suspect because they are so extensive when compared to their relatively muted criticisms for case-control studies, which, as I detail in the next sections, have their own significant weaknesses. For example, Dr. Smith-Bindman devotes several pages of her report to lodging numerous criticisms of each study that reported on cohort data; although she mostly spares Gertig 2000 (which happens to be the one cohort study she believes supports her theory), she declares in summary fashion that there is nothing "meaningful" to be gleaned from any of the other cohort studies.<sup>41</sup> Yet she provides no similar analysis of the strengths and weaknesses of the case-control studies, noting in the single paragraph in which she discusses them that her review and abstraction of data from them was done "[w]ithout assessing the[ir] quality."<sup>42</sup> Similarly, Dr. Moorman did not offer any criticisms or cautions regarding the talc meta-analyses, whereas she pointed out limitations of cohort studies extensively in her report.<sup>43</sup> None of the studies is perfect. But plaintiffs' experts' focused attack on cohort studies (as they seek to minimize the significant flaws of the case-control studies) reveals the biased and unscientific nature of their analyses.

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<sup>38</sup> Singh Rep. at 11, 53; McTiernan Rep. at 47.

<sup>39</sup> Houghton 2014 at 2.

<sup>40</sup> Gonzalez 2016 at 2.

<sup>41</sup> Smith-Bindman Rep. at 20-22.

<sup>42</sup> *Id.* at 29-30.

<sup>43</sup> Moorman Dep. 164:16-18; Moorman Rep. at 24-28.

In summary, none of the cohort studies found a statistically significant association between talc use and ovarian cancer.<sup>44</sup> The fact that these studies have shown uniformly null results indicates no association between talc use and ovarian cancer.

#### b. Results of Case-Control Studies

I have identified 25 population-based case-control studies addressing talc use and ovarian cancer.<sup>45</sup> The following table sets forth these studies' findings with respect to the association between ever/never talc use and ovarian cancer:

<sup>44</sup> Berge W, Mundt K, Luu H, Boffetta P. Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis. *Eur J Cancer Prev.* 2018; 27(3):248-257, 251 ("Berge 2018") (assigning a statistically insignificant 1.02 relative risk to the cohort studies in aggregate).

<sup>45</sup> Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: a case-control study. *Cancer.* 1982; 50(2):372-376; Harlow BL, Weiss NS. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *Am J Epidemiol.* 1989; 130(2):390-394; Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. *Obstet Gynecol.* 1992; 80(1):19-26 ("Harlow 1992"); Chen Y, Wu PC, Lang JH, et al. Risk factors for epithelial ovarian cancer in Beijing, China. *Int J Epidemiol.* 1992; 21(1):23-29; Cramer DW, Xu H. Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. *Ann Epidemiol.* 1995; 5(4):310-314; Purdie D, Green A, Bain C, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. *Survey of Women's Health Study Group. Int J Cancer.* 1995; 62(6):678-684; Chang S, Risch HA. Perineal Talc Exposure and Risk of Ovarian Carcinoma. *Cancer.* 1997; 79(12):2396-2401 ("Chang & Risch 1997"); Cook LS, Kamb ML, Weiss NS. Perineal Powder Exposure and the Risk of Ovarian Cancer *Am J Epidemiol.* 1997; 145(5):459-465 ("Cook 1997"); Green A, Purdie D, Bain C, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. *Survey of Women's Health Study Group. Int J Cancer.* 1997; 71(6):948-951; Godard B, Foulkes WD, Provencher D, et al. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *Am J Obstet Gynecol.* 1998; 179(2):403-410; Cramer DW, Liberman RF, Titus-Ernstoff L, et al. Genital Talc Exposure and Risk of Ovarian Cancer. *Int J Cancer.* 1999; 81(3):351-356 ("Cramer 1999"); Ness RB, Grisso JA, Cottreau C, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology.* 2000; 11(2):111-117; Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *Int J Cancer.* 2004; 112(3):458-464 ("Mills 2004"); Cramer DW, Titus-Ernstoff L, McKolanis JR, et al. Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 2005; 14(5):1125-1131; Jordan SJ, Green AC, Whiteman DC, Webb PM, Australian Ovarian Cancer Study Group. Risk factors for benign, borderline and invasive mucinous ovarian tumors: epidemiological evidence of a neoplastic continuum? *Gynecol Oncol.* 2007; 107(2):223-230; Gates 2008; Merritt MA, Green AC, Nagle CM, et al. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer.* 2008; 122(1):170-176 (2008) ("Merritt 2008"); Moorman PG, Palmieri RT, Akushevich L, et al. Ovarian cancer risk factors in African-American and white women. *Am J Epidemiol.* 2009; 170(5):598-606; Wu AH, Pearce CL, Tseng CC, et al. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *Int J Cancer.* 2009; 124(6):1409-1415 ("Wu 2009"); Rosenblatt KA, Weiss NS, Cushing-Haugen KL. Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes Control.* 2011; 22(5):737-742 ("Rosenblatt 2011"); Kurta ML, Moysich KB, Weissfeld JL, et al. Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. *Cancer Epidemiol Biomarkers Prev.* 2012; 21(8):1282-1292; Kotsopoulos J, Terry KL, Poole EM, et al. Ovarian cancer risk factors by tumor dominance, a surrogate for cell of origin. *Int J Cancer.* 2013; 133(3):730-739; Wu 2015; Cramer DW, Vitonis AF, Terry KL, et al. The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States. *Epidemiology.* 2016; 27(3):334-346 ("Cramer 2016"); Schildkraut JM, Abbott SE, Alberg AJ, et al. Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES). *Cancer Epidemiol Biomarkers Prev.* 2016; 25(10):1411-1417 (2016) ("Schildkraut 2016").

Author, Year	Ever/Never Results
Cramer 1982	RR 1.92 (95% CI: 1.27-2.89)
Harlow & Weiss 1989	RR 1.10 (95% CI: 0.70-2.10)
Harlow 1992	OR 1.50 (95% CI: 1.00-2.10)
Chen 1992	RR 3.90 (95% CI: 0.90-10.6)
Cramer & Xu 1995	OR 1.10 (95% CI: 0.60-2.10)
Purdie 1995	OR 1.27 (95% CI: 1.04-1.54)
Chang & Risch 1997	OR 1.42 (95% CI: 1.08-1.86)
Cook 1997	RR 1.60 (95% CI: 0.90-2.80)
Green 1997	RR 1.30 (95% CI: 1.10-1.60)
Godard 1998	RR 2.49 (95% CI: 0.94-6.58)
Cramer 1999	OR 1.45 (95% CI: 0.97-2.18)
Ness 2000	OR 1.50 (95% CI: 1.10-2.00)
Mills 2004	OR 1.37 (95% CI: 1.02-1.85)
Cramer 2005	OR 1.16 (95% CI: 0.90-1.49)
Jordan 2007	OR 1.00 (95% CI: 0.40-2.10)
Gates 2008	RR 1.36 (95% CI: 1.14-1.63)
Merritt 2008	OR 1.17 (95% CI: 1.01-1.36)
Moorman 2009	Afr. Am.: OR 1.19 (95% CI: 0.68-2.09) Caucasian: OR 1.04 (95% CI: 0.82-1.33)
Wu 2009	RR 1.53 (95% CI: 1.13-2.09)
Rosenblatt 2011	OR 1.27 (95% CI: 0.97-1.66)
Kurta 2012	OR 1.40 (95% CI: 1.16-1.69)
Kotsopoulos 2013 <sup>46</sup>	RR 1.19 (95% CI: 0.73-1.96)
Wu 2015	OR 1.46 (95% CI: 1.27-1.69)
Cramer 2016	OR 1.33 (95% CI: 1.16-1.52)
Schildkraut 2016	OR 1.44 (95% CI: 1.11-1.86)

I have identified seven hospital-based case-control studies addressing the association between talc use and ovarian cancer.<sup>47</sup> As set forth in the following table, none of these studies observed a statistically significant association:

<sup>46</sup> Study looked at all types of genital powder used at least once per week.

<sup>47</sup> Hartge P, Hoover R, Leshner LP, McGowan L. Talc and Ovarian Cancer. JAMA. 1983; 250(14):1844 (“Hartge 1983”); Whittemore AS, Wu ML, Paffenbarger RS Jr, et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. Am J Epidemiol. 1988; 128(6):1228-1240 (“Whittemore 1988”); Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. Br J Cancer. 1989; 60(4):592-598 (“Booth 1989”); Rosenblatt KA, et al. Mineral fiber exposure and the development of ovarian cancer. Gynecol Oncol. 1992; 45(1):20-25. (“Rosenblatt 1992”); Tzonou A, Polychronopoulou A, Hsieh CC, et al. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. Int J Cancer. 1993; 55(3):408-410 (“Tzonou 1993”); Hartge P, Stewart P. Occupation and ovarian cancer: a case-control study in the Washington, DC, metropolitan area, 1978-1981. J Occup Med. 1994; 36(8):924-927 (“Hartge & Stewart 1994”); Wong C, Hempling RE, Piver MS, et al. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. Obstet Gynecol. 1999; 93(3):372-376. (“Wong 1999”).

Author, Year	Ever/Never Results
Hartge 1983	RR 0.70 (95% CI: 0.40-1.10)
Whittemore 1988	RR 1.45 (95% CI: 0.81-2.60)
Booth 1989	RR 1.30 (95% CI: 0.80-1.90)
Rosenblatt 1992	OR 1.70 (95% CI: 0.70-3.90)
Tzonou 1993	RR 1.05 (95% CI: 0.28-3.98)
Hartge & Stewart 1994	RR 0.3 (95% CI: 0.1-1.4) to RR 0.5 (95% CI: 0.2-1.5) <sup>48</sup>
Wong 1999	OR 1.00 (95% CI: 0.80-1.30)

In summary, 11 of the 25 population-based case-control studies do not show a statistically significant association, and none of the hospital-based studies does. Notably, the authors of the case-control studies have generally cautioned that even when they found a statistically significant elevated risk, their results do not establish causation, even in combination with the results of other studies.<sup>49</sup>

### c. Results of Meta-analyses and Pooled Studies

Meta-analyses and pooled studies, which use statistical methods to pool results from different studies, have also been performed on the body of talc-ovarian cancer epidemiological literature. These studies have calculated an overall odds ratio of approximately 1.3,<sup>50</sup> which they have characterized as a “relatively weak odds ratio[]” that “can be attributed to bias in” case-control studies.<sup>51</sup> As some of these studies have stated, the epidemiological data are “insufficient

<sup>48</sup> This study did not provide a value for ever/never use; range reflects values across three strata of use durations.

<sup>49</sup> Cramer DW, Welch WR, Berkowitz RS, Godleski JJ, Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. *Obstet Gynecol.* 2007; 110(2 Pt 2):498-501, 500 (case study stating that “[w]e are not claiming that a causal relationship between ovarian cancer and talc use is proven for this case or in general”).

<sup>50</sup> Berge 2018 at 251 (RR 1.22 (95% CI: 1.13-1.30)); Terry KL, Karageorgi S, Shvetsov YB, et al. Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls. *Cancer Prev Res (Phila).* 2013; 6(8):811-821 (“Terry 2013”) (OR 1.24 (95% CI: 1.15-1.33)); Langseth 2008 (OR 1.40 (95% CI: 1.29-1.52)).

<sup>51</sup> Berge 2018 at 253; Cramer DW, Liberman RF, Titus-Ernstoff L, et al. Genital Talc Exposure and Risk of Ovarian Cancer. *Int J Cancer.* 1999; 81(3):351-356, 354 (“Cramer 1999”); Huncharek M, Geschwind JF, Kupelnick B. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. *Anticancer Res.* 2003; 23(2C):1955-1960 (2003 meta-analysis explaining that “[s]election bias and uncontrolled confounding may account for the positive associations seen in prior epidemiological studies”); Rothman KJ, Pastides H, Samet J. Interpretation of Epidemiologic Studies on Talc and Ovarian Cancer 4 (Nov. 28, 2000), <https://ntp.niehs.nih.gov/ntp/newhomeroc/roc12/mcewen-07-14-04.pdf> (“Recall bias can readily introduce enough bias to produce the modestly-sized overall effect (RR = 1.3) that emerges from these studies.”). I am aware of Dr. Zambelli-Weiner’s criticisms of the Huncharek studies, but Dr. Zambelli-Weiner does not claim that the studies understated the association between genital talc use and ovarian cancer; indeed, her efforts to replicate the dose-response calculations in Huncharek (2003) similarly failed to show a dose-response relationship.

to establish a causal association between perineal use of talc and ovarian cancer risk” and “not support[ive of] a causal interpretation of the association.”<sup>52</sup>

Plaintiffs’ experts rely on a 2018 study by Penninkilampi and Eslick, which conducted a literature review of studies addressing talcum powder use and ovarian cancer and performed a meta-analysis that “revealed an increased risk of ovarian cancer associated with any perineal use of talc (. . . OR = 1.31; 95% CI = 1.24, 1.39).”<sup>53</sup> Although the finding was statistically significant, it remains low, with a 1.31 odds ratio that falls within the range of prior studies, adding little to the existing literature on this question. Indeed, the authors acknowledged that several meta-analyses had been conducted by 2018, but sought to justify the need for another in light of ongoing litigation, contending that “the association between talc use and ovarian cancer [has taken] on considerable relevance” because “Johnson & Johnson has recently had damages levied to the total of US\$717 million against [it] in five law suits” and because “producers of talcum powder products continue to sell these products without any warning labels regarding perineal use and potential associations with ovarian cancer,” leading the authors to conclude that “there is a need for clarification, to allow women to be adequately informed of the risk of use of these products, possibly preventing future harm.”<sup>54</sup> This is an unusual statement in a scientific article and especially odd in an article that is ostensibly premised on the idea that existing science has not concretely defined the risk that the authors are suggesting should be warned against. The study is also puzzling in that its stated purpose is to update prior meta-analyses – in particular, because “the results of a number of large case-control studies and two cohort studies” had been reported since the last meta-analysis was published<sup>55</sup> – and yet the meta-analyses wholly excluded consideration of the Gates report (the NHS follow-up), another cohort study published during the same period. Ultimately, notwithstanding the authors’ expressed concerns about warning women and updating the research, their conclusions echo those of prior studies, acknowledging in some detail the possibility that recall bias drove the results in the case-control studies<sup>56</sup> and concluding that while the authors believe their results are “suggestive of a causal association,” it remains the case that “[a]dditional epidemiologic evidence from prospective studies with attention to effects within ovarian cancer subtype is warranted” and that “it is important that research into this association continue.”<sup>57</sup>

I also note that plaintiffs’ experts Dr. Smith-Bindman and Dr. Siemiatycki decided to conduct their own meta-analyses for purposes of their reports. I did not attempt such an undertaking because there is no need; there have been a number of recent meta-analyses in this area, and not enough new recent studies to justify running the same meta-analysis one more time

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<sup>52</sup> Langseth 2008 at 359; Berge 2018 at 256.

<sup>53</sup> Penninkilampi 2018 at 44.

<sup>54</sup> *Id.* at 42.

<sup>55</sup> *Id.*

<sup>56</sup> *Id.* at 47.

<sup>57</sup> *Id.* at 48.

(indeed, Dr. Siemiatycki acknowledges that the cumulative 1.28 relative risk his analysis generated is on par with those of the recent published meta-analyses).<sup>58</sup>

Dr. Smith-Bindman purports to have conducted her meta-analysis in an effort to specifically assess whether “regular” talc use causes ovarian cancer and serous invasive ovarian cancer in particular.<sup>59</sup> According to Dr. Smith-Bindman, a “narrow[er]” meta-analysis would offer the “most meaningful and consistent results,” ostensibly by reducing variation between the included studies as to “relevant factors such as age or race/ethnicity.”<sup>60</sup> But she does not cite any reference in support of her “less is more” theory; nor does she identify any generally accepted criticisms of existing talc meta-analytic work that would justify her narrower approach. She also offers no basis for concluding that the results of her study are somehow more reliable than the studies that have previously been done on the same body of literature, and which have been published after peer review. And indeed they are not, due to at least the following significant methodological deficiencies:

- Dr. Smith-Bindman states that she chose to focus on serous invasive ovarian cancer because it was the only subtype “for which most individual research studies accumulated sufficient cases for valid statistical analysis,” but she provides no analysis or data to support this claim.<sup>61</sup> Her decision to focus on serous invasive ovarian cancer (the only subtype that previously has been associated with an increased risk from talc in any of the cohort studies) illustrates a systematic exclusion of data that do not support her theory.
- Her concession that her measure of “regular” talc use was “subjective[]” is an understatement.<sup>62</sup> She defines “regular use” “ideally as daily or at least more than 3 uses per week,” but she also “accepted studies that defined use as ‘regular’ where the description made it clear that this was regular use.”<sup>63</sup> For some studies that reported “regular” use but sub-grouped that categorization, she only “included data for women in the highest use category,” and only if that group “was large enough to be meaningful.”<sup>64</sup> And when studies “asked about ever use but defined use and stratified results by use,” she “included any data that may have reflected daily use.”<sup>65</sup> Far too many questions arise from these vague and subjective criteria. For example, why did Dr. Smith-Bindman arbitrarily choose three uses per week as the lower threshold for regular use? Notably, this cut-off excluded the Gates study, which included data on women who used talc more

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<sup>58</sup> Siemiatycki Rep. at 41.

<sup>59</sup> *Id.* at 31.

<sup>60</sup> *Id.* at 30.

<sup>61</sup> *Id.* at 32.

<sup>62</sup> *Id.* at 34 (“I tried to be consistent in defining exposure, but this factor was subjectively determined by the individual studies.”); *see* Smith-Bindman Dep. Vol. II 272:3-273:3 (Smith-Bindman “tried to approximate regular use” and has not validated her metric).

<sup>63</sup> Smith-Bindman Rep. at 32.

<sup>64</sup> *Id.*

<sup>65</sup> *Id.*

than once per week (as explained below, including Gates in the meta-analysis would have lowered the odds ratio Dr. Smith-Bindman calculated for serous invasive). What criteria governed her determination of whether a study's description "made it clear" that it really addressed regular use? Why did she only use the highest use category when studies reported multiple categories of regular use, and what made such a group "large enough to be meaningful"? How did she determine "which data may have reflected daily use"? Although Dr. Smith-Bindman speculated at her deposition that other epidemiologists could repeat her analysis using her methodology,<sup>66</sup> the lack of a clear protocol and the need to reproduce seemingly arbitrary decisions in her assessment of "regular" talc use would make that very difficult, if not impossible. And importantly, whether a study reported on "regular" talc use appears to be the sole criterion Dr. Smith-Bindman employed in choosing studies for her review.

- Dr. Smith-Bindman excluded studies that examined talc use on sanitary napkins, diaphragms or condoms, claiming (without any supporting data) that perineal use is "the most common exposure type and is likely to reflect the most consistent exposure."<sup>67</sup> Notably, if the talc migration theory Dr. Smith-Bindman endorses is correct, data regarding talc use on condoms and diaphragms should be especially valuable, since such use introduces talc directly into the vagina. But studies examining such use have not reported an association with ovarian cancer, and her decision to exclude them again illustrates that she systematically avoided data that did not support her desired result.
- Even after designing a study selection methodology that enabled her to cherry-pick studies that supported finding an association, Dr. Smith-Bindman omitted Rosenblatt 2011 after initially selecting it.<sup>68</sup> That study reported negative associations between talc use and both invasive serous ovarian cancer and ovarian cancer overall for its two highest use categories.<sup>69</sup> At her deposition, Dr. Smith-Bindman speculated that she omitted this study because doing so did not make a difference in her results.<sup>70</sup> That is both an odd reason to exclude a study (all other things being equal, a more robust data set is obviously preferable) and objectively wrong, since her underlying data show that omitting the Rosenblatt study increased her odds ratio for frequent use and serous invasive from 1.38 to 1.52 and for frequent use and all ovarian cancer from 1.32 to 1.43.<sup>71</sup> In other words, if Dr. Smith-Bindman had not excluded Rosenblatt 2011 from her final results, she would

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<sup>66</sup> Smith-Bindman Dep. Vol. II 357:1-15; Smith-Bindman Dep. Vol. I 102:21-104:18; *see, e.g.*, Smith-Bindman Dep. Vol. I 197:19-198:6 (Smith-Bindman has no written protocol setting forth the myriad assumptions she and her colleague made when abstracting data).

<sup>67</sup> Smith-Bindman Rep. at 32-33.

<sup>68</sup> *Id.* at 33-34.

<sup>69</sup> Rosenblatt 2011 at Table 2 (reporting point estimates of 0.78 and 0.87 for invasive tumors and all tumors in women with between 4,800 and 9,999 lifetime applications; and 0.84 and 0.87, respectively, for women with more than 10,000 lifetime applications).

<sup>70</sup> Smith-Bindman Dep. Vol. I 177:20-180:13.

<sup>71</sup> TalcDataResults-janehall.xlsx (compare "All papers" tab with "Excluding Rosenblatt" tab).

not have been able to opine that regular talc use is associated with a 50 percent increase in the risk of serous invasive ovarian cancer.<sup>72</sup>

- The pool of studies on which she relies for her assessment of serous invasive ovarian cancer is very small – consisting of only four reports and far fewer cases overall than the broader pool of ovarian cancer studies, making the dataset less robust. Moreover, while Dr. Smith-Bindman includes the Gertig study as one of the four in her consideration of serous ovarian cancer risk, she omits the Gates study,<sup>73</sup> which, as noted above, updated the findings of the NHS on which Gertig had reported and concluded after ten more years of study that there was no association between talc use and serous ovarian cancer specifically (RR 1.06 (95% CI: 0.84-1.35)).<sup>74</sup> Had Gates been considered, Dr. Smith-Bindman's reported overall odds ratio of 1.52 for serous ovarian cancer would presumably have been much lower.
- As noted above, Dr. Smith-Bindman admittedly made no effort to assess the quality of the case-control studies that comprise 90 percent of her meta-analysis.<sup>75</sup> As she confirmed at her deposition, this included no effort to assess whether the studies she selected adequately controlled for bias and confounding.<sup>76</sup>
- Dr. Smith-Bindman admittedly abstracted inaccurate data from the studies she considered in her review.<sup>77</sup> Indeed, none of the confidence interval data she reports for the ten studies she includes in Figures 2 and 3 of her report match what was reported in the studies themselves.<sup>78</sup> This is surprising since Dr. Smith-Bindman acknowledges that data abstraction is an extremely important step for a meta-analysis and that having inaccurate

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<sup>72</sup> See Smith-Bindman Rep. at 34.

<sup>73</sup> *Id.*

<sup>74</sup> Gates 2010 at 50.

<sup>75</sup> Smith-Bindman Rep. at 29.

<sup>76</sup> Smith-Bindman Dep. Vol. II 311:18-312:24; *see id.* 284:7-15 (agreeing that bias in underlying studies does not disappear when they are combined in a meta-analysis).

<sup>77</sup> Smith-Bindman Dep. Vol. I 105:14-21.

<sup>78</sup> *Id.* 182:13-183:24. Compare Smith-Bindman Rep. at 33 fig. 2, with Booth 1989 at 596 (Smith-Bindman (0.75-1.85) vs. study (0.8-1.9)), and Chang & Risch 1997 at 2399 (Smith-Bindman (0.51-1.39) vs. study (0.61-1.49)), and Cook 1997 at 462 (Smith-Bindman (0.55-3.05) vs. study (1.2-2.9)), and Cramer 2016 at 335 (Smith-Bindman (0.97-2.01) vs. study (1.06-2.10)), and Gertig 2000 at 250 (Smith-Bindman (0.76-1.48) vs. study (0.82-1.55)), and Harlow 1992 at 19 (Smith-Bindman (0.85-2.75) vs. study (1.1-3.0)), and Mills 2004 at 460 (Smith-Bindman (0.93-2.55) vs. study (1.14-2.64)), and Schildkraut 2016 at 1413 (Smith-Bindman (1.18-2.24) vs. study (1.26-2.33)), and Whittemore 1988 at 1231 (Smith-Bindman (0.81-2.09) vs. study (0.81-2.60)), and Wu 2009 at 1409 (Smith-Bindman (1.14-3.02) vs. study (1.34-3.23)). Compare Smith-Bindman Rep. at 34 fig. 3, with Chang & Risch 1997 at 2399 (Smith-Bindman (1.07-1.96) vs. study (1.13-2.02)), and Cook 1997 at 462 (Smith-Bindman (0.55-3.05) vs. study (1.2-2.9)), and Cramer 2016 at 342 (Smith-Bindman (1.08-2.00) vs. study (1.15-2.07)), and Gertig 2000 at 250 (Smith-Bindman (0.86-2.12) vs. study (0.98-2.26)).

data can compromise a meta-analysis.<sup>79</sup> Dr. Smith-Bindman also admits that she likely double-counted patients in her data, despite acknowledging that this should be avoided.<sup>80</sup>

In short, Dr. Smith-Bindman's meta-analysis is arbitrary, error-laden and designed to systematically exclude data that do not support the theory that talc use causes ovarian cancer. These methods are unreliable. Based on her meta-analysis, Dr. Smith-Bindman concluded that she does "not have *any uncertainty* that regular exposure to talc powder products" increases the risk of ovarian cancer;<sup>81</sup> yet, it is difficult to conceive how use of such a methodology would not introduce *substantial uncertainty* into a meta-analysis, as well as any interpretation of its results.

## 2. Bias

Bias is a particularly important issue when analyzing whether perineal exposure to talcum powder causes ovarian cancer because, as set forth above, the reported risks are very small. The reporting of small risks suggests these studies are susceptible to biases.<sup>82</sup>

Additionally, case-control studies are particularly susceptible to bias (although I agree with Dr. McTiernan that hospital-based studies may be less distorted by recall bias than population-based studies because the former feature both ill cases and ill controls).<sup>83</sup> In most of the case-control studies pertaining to perineal talcum powder use and ovarian cancer, the authors discuss the potential for bias, including recall bias. However, only one study examined the issue directly, and it found striking and clear evidence of the impact of recall bias on the study results.

In the case-control study reported by Schildkraut et. al., the authors (including Dr. Moorman) considered that "the possibility of differential misclassification exists in a case-control study such as AACES, especially due to the heightened awareness of the exposure as a result of" well-publicized litigation.<sup>84</sup> The investigators examined their finding based on whether the study subjects were interviewed before 2014 versus 2014 onward. Among those interviewed before 2014, the reported use of body powder on the genitals was nearly the same for cases and controls (36.5 and 34.0%, respectively). But from 2014 onward, the reported use among cases was markedly higher (51.5%), while it stayed the same in controls (34.4%). This striking and abrupt change in reporting clearly demonstrates the major impact of recall bias, and that plaintiffs' experts are wrong to label recall bias in case-control studies "theoretical."<sup>85</sup> But it also calls into question earlier results because – contrary to Dr. Moorman's claim that "the vast

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<sup>79</sup> Smith-Bindman Dep. Vol. I 104:22-105:13, 106:6-13; Smith-Bindman Dep. Vol. II 282:16-283:3.

<sup>80</sup> Smith-Bindman Rep. at 34; Smith-Bindman Dep. Vol. II 344:9-345:3.

<sup>81</sup> Smith-Bindman Rep. at 4 (emphasis added).

<sup>82</sup> Moorman Dep. 251:2-7 ("I think that with a smaller association, there is more concern that it could be due to bias from various reasons.").

<sup>83</sup> McTiernan Rep. at 24

<sup>84</sup> Schildkraut 2016 at 1416.

<sup>85</sup> McTiernan Rep. at 20; Moorman Rep. at 23.

majority of studies” were not affected by this issue<sup>86</sup> – the question of talc and ovarian cancer did not emerge for the first time in 2014, and earlier studies could well have been affected by a more modest but nonetheless significant recall bias. Clearly, media reporting about talc and ovarian cancer did not begin in 2014; rather, there are multiple news reports between 1982 and 2013 (**See Appendix A: Sample Of Pre-2014 News Articles Addressing Posited Link Between Talc Use And Ovarian Cancer for a list of examples**). Women with ovarian cancer in that era could easily have been influenced in their recall of talcum powder use, which would potentially amplify recall bias in pre-2014 studies as well.

Dr. Moorman further argues that “empirical evidence” shows that recall bias in case-control studies is only a theoretical concern, citing a study by Lanza et al. that found that case-control and cohort studies reached similar results regarding certain therapeutic interventions.<sup>87</sup> But the Lanza findings (which had nothing to do with talc) are obviously not applicable to the situation here, where the case-control and cohort studies at issue have been highly heterogeneous.<sup>88</sup>

Other study authors have recognized the problem of bias in their studies as well. For example, a 2017 pooled study of 12 case-control studies addressing ovarian cancer risk factors in four ethnic groups found a statistically significant elevated risk for talc use among two of the four ethnic groups (Non-Hispanic White (OR 1.30 (95% CI: 1.20–1.41)) and Black (OR 1.62 (95% CI: 1.32–2.00)) and no statistically significant elevated risk for the other two groups (Hispanic (OR 1.41 (95% CI: 0.93–2.13)) and Asian/Pacific Islander (OR 1.02 (95% CI: 0.61–1.70))).<sup>89</sup> The authors characterized the differences across groups as “[s]tudy heterogeneity” and cautioned: “A concern with self-reported data is recall bias, especially for characteristics that are difficult to report with accuracy, require subjective summarization or can be influenced by the investigator, media or similar factors. Such problematic characteristics may include body powder exposure[.]”<sup>90</sup>

### 3. Confounding

Similarly, confounding factors may have affected the studies that found a small estimated risk pertaining to perineal exposure to talcum powder and ovarian cancer. This issue is especially concerning when it comes to ovarian cancer risk because, generally, scientists do not know the cause of ovarian cancer.<sup>91</sup> Thus, even studies that attempt to account for known confounders (such as familial or genetic risk) likely do not account for most of the risks – known or unknown.

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<sup>86</sup> Moorman Rep. at 23.

<sup>87</sup> Moorman Rep. at 23; Moorman Dep. 227:11-23.

<sup>88</sup> See Moorman Dep. 227:24-232:15.

<sup>89</sup> Peres LC, Risch H, Terry KL, et al. Racial/ethnic differences in the epidemiology of ovarian cancer: a pooled analysis of 12 case-control studies. *Int J Epidemiol.* 2018; 47(2):460-472.

<sup>90</sup> *Id.* at 8-9.

<sup>91</sup> Siemiatycki Dep. 173:6-9 (agreeing that “all of the factors that might make someone susceptible to developing ovarian cancer are not currently known”).

The Sister Study<sup>92</sup> provides insight into one potential source of confounding in prior studies. In that study, the investigators accounted for douching, an exposure not considered in nearly all other studies. The authors were interested in douching because of concerns that it could “introduce particles and toxicants in the upper reproductive tract and increase the risk of cancers and infections.” They cited evidence that douching products contain phthalates that “could influence ovarian cancer risk through hormone disruption.” The study found that douching was a risk factor for ovarian cancer (HR 1.8 (1.2-2.8)), while talc use was not (HR 0.73 (0.44-1.2)). Douching, with or without concurrent talc use, had similar risk (HR 1.8 and 1.9, respectively). The investigators noted that the practice of douching and talc use are correlated and that “if douching is a risk factor for ovarian cancer, some of the earlier reports on talc could have been subject to confounding bias.” The same study also showed that douche users are different from non-users, with users more likely being Non-Hispanic Black, of lower educational attainment and/or obese. These systematic differences highlight the complexity of understanding the potential effect of a non-random feminine hygiene practice and judging causation when estimated risks are otherwise so small.

The finding in Gonzalez that the douche users had lower educational attainment suggests that socioeconomic status may be another important confounder. Indeed, in another study by Alberg et al. the investigators found that higher educational attainment may be protective against developing ovarian cancer (or in other words, low educational attainment is associated with higher risk of developing ovarian cancer).<sup>93</sup> The authors noted that if socioeconomic status is truly protective, the reasons for the relationship still need to be identified.<sup>94</sup> They suggested that differences in diet and exercise could be related to risk, which overall means that assessing confounding in ovarian cancer studies is important, complex and not yet fully developed in research.<sup>95</sup> What is important in assessing the epidemiologic studies of talc and ovarian cancer is that, as Dr. Smith-Bindman acknowledges, the studies did not use a uniform approach to assessing confounders, with, for example, nearly all not adjusting for douching and many not accounting for education or socioeconomic status.<sup>96</sup> Accordingly, Dr. McTiernan’s argument that confounding is unlikely because studies have reported small differences between adjusted and crude results is overly simplistic (and in any event ignores that studies cannot adjust for unknown confounders).<sup>97</sup>

#### 4. Other Considerations

It is important to recognize that the strength of an association is not the same as the importance of the association. The importance of an association is based on the judgment of

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<sup>92</sup> Gonzalez 2016.

<sup>93</sup> Alberg AJ, Moorman PG, Crankshaw S, et al. Socioeconomic Status in Relation to the Risk of Ovarian Cancer in African-American Women: A Population-Based Case-Control Study. *Am J Epidemiol.* 2016; 184(4):274-283.

<sup>94</sup> *Id.* at 282.

<sup>95</sup> *Id.*

<sup>96</sup> Smith-Bindman Dep. Vol. II 307:21-308:24.

<sup>97</sup> McTiernan Rep. at 24; McTiernan Dep. 176:17-177:23.

those using the information. A new medication that reduces death from heart attacks by 2% may be judged to be very important, and if that drug causes itching in 30% of users, that finding may be judged less important. An effect that is judged to be important is not evidence of causation, however.

In this matter, some of plaintiffs' experts have provided confusing opinions about strength of association. While the strength of association between talcum powder use and ovarian cancer is indisputably small, the experts have nevertheless found it to be "strong" by discussing their judgments about the potential importance of the findings and also by bringing in other arguments, such as statistical significance. For example, Dr. Smith-Bindman states:

"It is frequently argued that the larger an apparent association, the more likely the association is to be real (causal) and important for epidemiological assessment. This would suggest that an OR of 2.0 is more likely to indicate causality and importance than an OR of 1.5. While this is often argued, I do not believe this is necessarily the case. If a risk factor increases the risk of disease by 50%, and the exposure is common, it will have far greater impact on a number of people, in comparison to a rare exposure that has a higher associated OR. A larger association between exposure and disease may be easier to identify, but I do not believe it is more likely to indicate causality or importance."<sup>98</sup>

Dr. Smith-Bindman is conflating the distinct issues of causation and importance in arguing that "the data supporting the causality of talcum powder products exposure for ovarian cancer is extremely strong."<sup>99</sup> She goes on to calculate the number of ovarian cancers she believes are caused by talcum powder products and uses this calculated number of cancers to support her statement that "this Bradford Hill Factor of the Strength of the association is important and met."<sup>100</sup> In other words, Dr. Smith-Bindman opines that because, according to her calculations, a large percentage of ovarian cancer is caused by talcum powder, the association is "strong." This statement is misleading and circular because Dr. Smith-Bindman is using the "importance" of the finding, which is only important if true (i.e., causal), to support the judgment that the very small association is causal. One needs to first determine if an association is causal, and only then, if it is causal, decide on its importance.

Other plaintiffs' experts make similar conflated arguments. Dr. Blair Smith uses the potential importance of the finding in her assessment of the strength of association when she states that "there is no set magnitude or threshold for ascribing causality. I would maintain that any practice or element that increases the risk of ovarian cancer by ANY consistent percentage is significant."<sup>101</sup> Dr. Moorman also states that it is "critical to consider the prevalence of the exposure" in assessing strength of association and "how many cases of disease could be

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<sup>98</sup> Smith-Bindman Rep. at 36.

<sup>99</sup> *Id.* at 37.

<sup>100</sup> *Id.* at 38.

<sup>101</sup> Blair Smith Rep. at 19.

attributable to this exposure.”<sup>102</sup> Likewise, Dr. McTiernan, although admitting the risks are approximately 22-31% (equivalent to RR ~1.2-1.3), expressed the opinion that the association is strong because “given the high prevalence of use of talcum powder products” in this population, these levels of risk present a clinically significant public health concern.”<sup>103</sup> Thus, Drs. Blair Smith and McTiernan are using the concept of importance to justify the strength of a very small numerical risk. Furthermore, Dr. McTiernan’s opinion about the strength of association is confusing for the additional reason that she folds in other criteria such as consistency of findings, which should be assessed separately. Dr. McTiernan’s conflation of many different concepts makes her Bradford Hill analysis unreliable.

Plaintiffs’ experts also cite to examples of “established carcinogens” with similar estimates of strength of association – like passive smoke exposure and lung cancer, or hormone replacement therapy and breast cancer – to conclude that the association between talc and ovarian cancer is strong enough to be causative.<sup>104</sup> Although it is true that the associations are numerically similar, it is improper to conclude that any association of the same size is causal. After all, for those other exposures, the fact of a weak association may have been overcome by strong evidence that the other Bradford Hill criteria were met. And, as Dr. Moorman concedes, there are also examples of numerically similar associations that have not been established as causal.<sup>105</sup> Additionally, causation for certain of these other examples was based on data from randomized trials, which are the strongest evidence of a causal relationship. For example, the clinical trials pertaining to hormone therapy and breast cancer randomly assigned patients to treatment and control groups, rendering a high likelihood that any association that is observed is due to the exposure, as opposed to bias or confounders. In other words, the causal relationship between hormone therapy and breast cancer is based on better data, not on the finding of a small association.<sup>106</sup>

Additionally, plaintiffs’ experts’ heavy reliance – and in the case of Dr. McTiernan, exclusive reliance<sup>107</sup> – on meta-analyses and pooled analyses to demonstrate strength of association is flawed in many respects. First, as plaintiffs’ experts have repeatedly acknowledged, the meta-analyses do not eliminate the bias inherent in the underlying studies.<sup>108</sup> And although plaintiffs’ experts focus on newer studies,<sup>109</sup> Dr. Siemiatycki admits that the

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<sup>102</sup> Moorman Dep. 261:1-262:1.

<sup>103</sup> McTiernan Rep. at 9.

<sup>104</sup> Singh Rep. at 17; Moorman Rep. at 12; Moorman Dep. 245:10-16; Siemiatycki Dep. 148:8-19.

<sup>105</sup> Moorman Dep. 255:12-25 (“I acknowledge that – of course, that there are reports of exposures that have reported relative risk in this range, and it could either be something that was associated with another risk factor and it was not the causal factor or the level of evidence was not adequate.”).

<sup>106</sup> Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women’s Health Initiative Randomized Trial. JAMA. 2003; 289(24):3243-3253.

<sup>107</sup> McTiernan Rep. at 63; McTiernan Dep. 243:7-14.

<sup>108</sup> McTiernan Dep. 244:9-13; Moorman Dep. 159:8-160:18.

<sup>109</sup> McTiernan Dep. 282:2-4.

relative risks have gone down as more data has been collected over the years. For example, the 1.28 odds ratio provided by Dr. Siemiatycki in his 2018 meta-analysis is lower than the 1.35 relative risk published in the 2008 Langseth article.<sup>110</sup> And Dr. Siemiatycki acknowledged that the Berge 2018 authors noted a downward trend in the risk assessment over time.<sup>111</sup>

Finally, Dr. Smith-Bindman reports finding a slightly higher odds ratio of 1.52 by focusing on the particular histologic subtype of serous ovarian cancer.<sup>112</sup> But this alternative approach to the issue of strength does not materially affect the analysis. An odds ratio of 1.52 remains well below 2.0 and would still be considered a weak association. The studies offering odds ratios for serous ovarian cancer, like the broader pool of studies, contain a mix of findings, with some reporting statistically significant findings and others not.<sup>113</sup> And Dr. Smith-Bindman's methodology to reach the 1.52 odds ratio was deficient for the numerous reasons discussed above.

Based on the foregoing, it is my opinion that the association between perineal talcum powder exposure and ovarian cancer is weak and likely impacted by bias, confounding and/or chance. Moreover, plaintiffs' experts' attempts to explain away these problems and cast the science as standing for essentially the opposite proposition – that the epidemiology establishes a strong or conclusive association – strongly suggest that they are engaged in advocacy rather than science.

#### **B. Epidemiologic Studies Are Inconsistent.**

As set forth above, the prospective epidemiologic studies (cohort studies) do not show a statistically significant association, while only a subset of the population-based case-control studies does.<sup>114</sup> This disparity reflects inconsistent results across different types of studies, undermining the conclusion that cosmetic talc use causes ovarian cancer. The fact that none of the cohort studies found a statistically significant association between talc use and ovarian cancer is critical in this regard,<sup>115</sup> because it calls into doubt even the modest association in some of the population-based case-control studies.

Other inconsistencies exist in the literature as well, including some that overlap with the concepts of coherence and plausibility.<sup>116</sup> Evaluating an association with the use of talc-dusted

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<sup>110</sup> Siemiatycki Dep. 149:14-150:3.

<sup>111</sup> Siemiatycki Dep. 206:21-207:19.

<sup>112</sup> Smith-Bindman Rep. at 34.

<sup>113</sup> *Id.* at 34 fig. 3 (citing four studies, one of which (Cook 1997) reported a statistically insignificant result, and two of which have confidence intervals that are only barely above 1.0).

<sup>114</sup> As just explained, this disparity holds for the subtype of serous ovarian cancer as well, as to which the Gates study reported no statistically significant association.

<sup>115</sup> Berge 2018 at 251.

<sup>116</sup> Fiume MM, Boyer I, Bergfeld WF, et al. Safety Assessment of Talc as Used in Cosmetics. *Int J Toxicol.* 2015; 34(1 Suppl):66S-129S, 119S ("Fiume 2015"); Hartge 1983; Muscat JE, Huncharek MS. Perineal talc use and

diaphragms and condoms has been deemed “the most valid method for testing the carcinogenic potential of talc” because “[b]y definition, the female reproductive tract is exposed to talc containing powders introduced by diaphragms, whereas an exposure route based on perineal dusting requires unproven assumptions about vaginal exposure.”<sup>117</sup> Studies pertaining to use of talcum powder on diaphragms and condoms have shown a consistent lack of risk. It is illogical that talcum powder applied to the outside of the genital tract can cause ovarian cancer, while talcum powder applied inside the genital tract would not. Additionally, assertions by plaintiffs’ experts that these studies are “obsolete” due to a “lower methodological quality”<sup>118</sup> are merely unfounded assertions.

Some of plaintiffs’ experts still argue that the data on the association between genital talc use and ovarian cancer are highly consistent, but their explanations fail.

For example, Dr. McTiernan states that “[a]cross the case-control and cohort studies, the association between use of talcum powder products and risk of ovarian cancer was highly consistent.”<sup>119</sup> This statement is simply not true: while some of the case-control studies have shown a small positive risk, the cohort studies have uniformly failed to demonstrate a risk, as Dr. McTiernan admits.<sup>120</sup> She states further that because the cohort studies “were not well designed to determine true risk for ovarian cancer and perineal talc use their results as a group do not negate the significant case-control findings.”<sup>121</sup> But her criticisms of cohort studies are misplaced, as previously discussed. In any event, her argument assumes that the results of some studies are not consistent, or else there would be no reason for Dr. McTiernan to find fault with the cohort study designs in order to explain why their results do not negate the findings from other studies. Furthermore, Dr. McTiernan completely ignores the fact that within the case-control studies, there is evidence of inconsistency based on the type of control group. The different findings in the case-control studies by type of control group is further evidence of inconsistency.

Drs. Singh and Moorman purport to find consistency because “[t]he meta-analysis of case-control studies has consistently shown a statistically significant increased risk” and “the meta-analysis of cohort studies has also shown an excess risk, [] which failed to reach statistical significance.”<sup>122</sup> This consistency analysis is faulty for two reasons. First, since meta-analyses

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ovarian cancer: a critical review. *Eur J Cancer Prev.* 2008; 17(2):139-146, 144-145 (2008) (“Muscat & Huncharek 2008”).

<sup>117</sup> Muscat & Huncharek 2008.

<sup>118</sup> Singh Rep. at 17, 26-27.

<sup>119</sup> McTiernan Rep. at 64.

<sup>120</sup> McTiernan Dep. 200:25-201:10 (“So yes, there was heterogeneity between the case-control and cohort studies”), 202:17-203:1 (“I agree that the cohort studies have lower relative risks than do the case-control studies, yes.”).

<sup>121</sup> McTiernan Rep. at 64.

<sup>122</sup> Singh Rep. at 17; Singh Dep. 146:25-147:5 (stating “[t]he cohort studies show . . . increased risk, which is in the same direction as the case-control studies”); Moorman Dep. 262:20-264:13 (explaining that “both the Houghton study and the Nurses’ Health Study . . . are consistent in terms of the direction of the effect”).

analyze overlapping sets of individual studies, it is not surprising that meta-analyses yield consistent results. For this reason, consistency as determined by the meta-analyses' estimates is not supportive of Bradford Hill's consistency of association criterion. Second, as Drs. Singh and Moorman admit, the purported "excess risk" or "direction of the effect" shown in the meta-analyses of cohort studies does not amount to "statistical significance."<sup>123</sup> Drs. Singh and Moorman's classification of "excess risk" or "direction of the effect" glosses over the fact that case-control studies and cohort studies found varying strengths of association that do not amount to consistent results. Similarly, Dr. McTiernan's purported assessment of consistency by "look[ing] at whether the relative risk is above one consistently" is so broad that it is nonsensical, as it would consider near-null associations and definitively causal associations consistent.<sup>124</sup> And plaintiffs' experts' argument that certain studies would have shown a statistically significant increased risk if they had larger sample sizes (i.e., Dr. McTiernan with respect to cohort studies and Dr. Moorman with respect to small, non-statistically significant associations in African American and white women found in her 2009 study)<sup>125</sup> is speculative because there is no way to know whether a larger sample would provide the same or a different estimate or whether that estimate would be statistically significant. I note that the fact that Dr. Moorman did not include these results from her own 2009 study in her report suggests a biased approach to synthesizing the literature.<sup>126</sup> In any event, Drs. McTiernan and Moorman likewise ignored the Berge study's analysis demonstrating that the cohort studies collectively had sufficient power to detect a 1.25 relative risk if one existed; as the authors stated, "low power of cohort studies cannot be invoked as [an] explanation of the heterogeneity of results."<sup>127</sup>

**C. Specificity Is Not Compelling.**

Specificity was not considered very important by plaintiffs' experts and I agree.<sup>128</sup> There is no compelling case for specificity here either.

**D. The Epidemiological Data Do Not Show Biological Gradient (Dose Response).**

**1. Available Epidemiological Data On Dose-Response**

Evidence of dose-response – i.e., whether the risk of developing ovarian cancer increases with increased perineal talc exposure – is one of the most important factors to consider in

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<sup>123</sup> Moorman Dep. 266:6-16.

<sup>124</sup> McTiernan Dep. 212:17-21; *see* McTiernan Rep. at 44 (considering the near-null and not statistically significant 1.06 odds ratio reported in Houghton 2014 evidence of consistency of association); Moorman Dep. 263:13-264:13 (similar).

<sup>125</sup> McTiernan Rep. at 45-46; Moorman Dep. 136:12-19.

<sup>126</sup> Moorman Dep. 136:21-137:2; *see* Moorman PG1, Palmieri RT, Akushevich L, et al. Ovarian cancer risk factors in African-American and white women. *Am J Epidemiol.* 2009; 170(5):598-606 (reporting non-statistically significant odds ratios of 1.19 and 1.04 for African American and white women, respectively).

<sup>127</sup> Berge 2018 at 253; *see* Moorman Dep. 213:2-23; McTiernan Rep. at 46-47.

<sup>128</sup> Singh Rep. at 64.

evaluating causation. The epidemiological literature studying talc and ovarian cancer has failed to show a dose-response relationship. Plaintiffs' experts claim that there is sufficient data supporting the existence of a dose-response relationship<sup>129</sup> and have pointed to some studies as purported evidence of dose-response, including, for example, the articles by Schildkraut and Cramer.<sup>130</sup> But overall, the literature is very inconsistent with regard to dose-response, as Drs. Smith-Bindman and Moorman concede.<sup>131</sup>

None of the cohort studies (Gonzalez 2016; Houghton 2014; and Gates 2010/Gertig 2000) demonstrates a dose-response relationship, and only a handful of case-control studies (Harlow et al. 1992; Cramer 2016 and Schildkraut 2016) have purported to find one. The case-control studies have in fact shown a wide variety of findings, including: (1) a positive dose-response; (2) no dose-response; (3) a negative dose-response; and (4) a haphazard or bizarre pattern. Notably, among the numerous case-control studies that have not reported a dose-response relationship are several studies that have analyzed "cumulative" talc use (otherwise known as "frequency times duration" of use). For example, Mills 2004 examined cumulative dose by quartiles and reported risks of 1.03, 1.81, 1.74 and 1.06 for ascending quartiles – a bizarre trend that does not support there being a dose response.<sup>132</sup> Similarly, the Cook 1997 study looked for an association across various strata of "cumulative lifetime days."<sup>133</sup> The results showed no statistically significant elevated risk for any of the four categories, with the relative risk for the lowest group (fewer than 2,000 cumulative days, RR 1.8 (95% CI: 0.9-3.5)) essentially matching that of the highest group (greater than 10,000 cumulative days, RR 1.8 (95% CI: 0.9-3.4)).<sup>134</sup> Moreover, as noted above, the Rosenblatt 2011 study looked at the association across four categories of increasing lifetime applications and reported the lowest associations (in fact, negative associations) for its two highest use categories.<sup>135</sup> In addition, Chang found an inverse relationship with risks related to use per month of 1.8, 1.1 and 0.9 for respectively <10, 10-25 and more than 25 applications; similar inverse findings for years of use were 1.7, 1.4 and 0.86 for <30, 30-40 and >40 years of use.<sup>136</sup>

Although some studies have purported to observe a dose trend with cumulative use, those results are not meaningful. For example, the Schildkraut study only compared women who had used talc fewer than 20 years versus more than 20 years and fewer than 3600 applications versus

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<sup>129</sup> Singh Rep. at 55-56; Smith-Bindman Rep. at 39-40.

<sup>130</sup> Singh Rep. at 56.

<sup>131</sup> Smith-Bindman Rep. at 40 ("most but not all studies of talcum powder products and ovarian cancer show a dose response, but the results are inconsistent, and more importantly, are not considered or assessed in most of the published studies"); Moorman Dep. 272:5-10 ("across the studies, some have found a dose-response, some have not").

<sup>132</sup> Mills 2004.

<sup>133</sup> Cook 1997 at 463.

<sup>134</sup> *Id.*

<sup>135</sup> Rosenblatt 2011 at 740.

<sup>136</sup> Chang & Risch 1997.

more than 3600 applications.<sup>137</sup> Although it found statistically significant associations for the higher but not lower use categories, the study provides little useful information about dose-response because exposure is crudely dichotomized into just two categories each for frequency and duration. And the Cramer study found essentially no difference – and certainly no steady increase – in risk as to women who had (as the study calculated) used talc for the equivalent of 1-5 years, 5-20 years and more than 20 years (odds ratios of 1.36, 1.41 and 1.39, respectively).<sup>138</sup>

Several meta-analyses and pooled studies have analyzed the body of studies and resoundingly concluded that there is not a demonstrated dose response. For example, the 2013 Terry pooled study of eight case-control studies addressed the potential association between ovarian cancer and the use of powder (broadly defined to include both talc and cornstarch).<sup>139</sup> One of the primary goals of the analysis was to determine whether a dose-response relationship existed, as previous evidence “ha[d] been inconsistent.”<sup>140</sup> The authors found that it did not.<sup>141</sup> Indeed, although Dr. Siemiatycki claims that this study is “the most important evidence around dose-response,” the authors stated that they “observed ***no significant trend in risk with increasing number of lifetime applications***,” as he has acknowledged.<sup>142</sup> The Terry study, in fact, only observed a positive dose trend when including non-talc users in the analysis,<sup>143</sup> which is not actually meaningful evidence of a dose response, since including nonusers in a dose-response analysis makes that analysis redundant with whether there is an association with ever/never use, as Dr. Siemiatycki acknowledges.<sup>144</sup> Although Dr. Siemiatycki argues that it may be appropriate to include nonusers in the dose-response analysis when a study only reports on dose-response and not ever/never use,<sup>145</sup> that clearly does not apply to the Terry study, which reported on both types of data. Of note, the Terry authors did not mention the trend with nonusers in their abstract or discussion, instead highlighting that they found “no significant [dose] trend” and explaining that “[w]hether risk increases with number of genital powder applications and for all histologic types of ovarian cancer . . . remains uncertain.”<sup>146</sup> The authors also acknowledged that, if anything, the study might ***overstate*** the relationship between powder use and ovarian cancer if cases [i.e., women with ovarian cancer] were more likely to report

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<sup>137</sup> Schildkraut 2016 at 1415-1416 (Table 2).

<sup>138</sup> Cramer 2016 at 337 (Table 1).

<sup>139</sup> Terry 2013 at 812.

<sup>140</sup> *Id.*

<sup>141</sup> *Id.*

<sup>142</sup> *Id.* at 811, 812 (emphasis added); Siemiatycki Dep. 197:17-22, 266:8-15, 268:14-21.

<sup>143</sup> Terry 2013 at 817.

<sup>144</sup> Siemiatycki Rep. at 43 (“If the Ever/Never result is presented and then a dose-response analysis is conducted, it is preferable to maintain statistical independence of the two analyses by excluding the baseline unexposed category from the dose-response analyses).

<sup>145</sup> *Id.*

<sup>146</sup> Terry 2013 at 811, 819-20.

genital-powder use than controls [i.e., women without ovarian cancer].”<sup>147</sup>

Similarly, a 2008 meta-analysis identified “the absence of clear exposure-response associations in most studies” as a crucial piece of missing evidence needed to establish causation.<sup>148</sup> And in assessing the body of literature, the National Cancer Institute (“NCI”) and the United States Food & Drug Administration (“FDA”) have respectively concluded that “a dose response relationship was not found” and that “dose-response evidence is lacking.”<sup>149</sup> Although two more recent meta-analyses claimed to find evidence of a very small dose-response, these data are not compelling. Specifically, Berge 2018 reported a “weak” dose-response trend, but cautioned that these data came from a small number of case-control studies.<sup>150</sup> And Penninkilampi divided talc users into only two categories (greater and fewer than 3,600 lifetime applications), finding only a “slightly greater increased risk” for the former category (also based only on case-control data).<sup>151</sup> As with Schildkraut, the arbitrary dichotomous categorization of lifetime use further undercuts the significance of this finding.

Consistent with these results, pathological studies have not reported a correlation between the amount of talc used and talc particle counts in ovaries. As one study explained: “ovarian talc particle burden has been found not to correlate with the reported number of lifetime applications, which (if not reflective of inaccurate reporting) may indicate that duration of the powder use is not relevant when assessing risk associated with differing levels of exposure to talc.”<sup>152</sup>

In sum, the findings of so many different patterns, or lack of patterns, by dose-response estimation weighs against causation, and indeed, the fact that the data show no clear dose trend is consistent with there being no causal relationship. If one were to believe that perineal talcum powder use causes ovarian cancer, these mixed and inconsistent results should cast serious doubt

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<sup>147</sup> *Id.* at 820.

<sup>148</sup> Langseth 2008 at 359; *see* Gertig 2000 at 249, 251 (cohort study concluding that “[w]e did not observe a dose-response relationship with talc use, and previous studies have been inconsistent in this regard”); Cramer 1999 at 355 (case-control study by Dr. Daniel Cramer conceding that “[t]he most obvious weakness in the argument for biologic credibility of the talc and ovarian cancer association is the lack of a clear dose response” and that “[m]ost talc and ovarian cancer studies that have addressed dose response, including this one, have failed to demonstrate consistent dose response relationships”).

<sup>149</sup> National Cancer Institute, Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ®)—Health Professional Version, <https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq> (last updated Jan. 4, 2019); Letter from Food & Drug Administration, U.S. Department of Health and Human Services, to Samuel S. Epstein, M.D., Cancer Prevention Coalition, University of Illinois (Apr. 1, 2014); International Agency for Research on Cancer, Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 93: Carbon Black, Titanium Dioxide, and Talc 18-19 (2010) (“IARC Talc Monographs”) (concluding that evidence of a dose-response relationship was “inconsistent”).

<sup>150</sup> Berge 2018 at abstract, 255.

<sup>151</sup> Penninkilampi 2018 at 45.

<sup>152</sup> Rosenblatt 2011 at 742 (discussing Heller DS, Westhoff C, Gordon RE, Katz N. The Relationship Between Perineal Cosmetic Talc Usage and Ovarian Talc Particle Burden. *Am J Obstet Gynecol.* 1996; 174(5):1507-1510 (“Heller 1996”)).

on the validity of the measures used to estimate whether and how much talcum powder was used.

## 2. Validity Of Exposure Measure

In epidemiologic research, it is critical to assess exposures of interest with accuracy and precision. This includes measuring exposures with tools that have demonstrable validity. Without a validated measure of exposure, it is not possible to know whether or not an exposure occurred, and even if it did, it is not possible to quantify the exposure with any degree of certainty.

While there is a scientific approach for development and testing of survey questions for use in research,<sup>153,154,155</sup> there is not a single epidemiologic study of the potential association between perineal use of cosmetic talcum powder and ovarian cancer that has used, or purports to have used, a validated measure of talcum powder use.<sup>156</sup> Thus, it is unknown whether any of the studies have accurately assessed whether talcum powder was used, for how long and how frequently. Self-report measures can be highly inaccurate, and none has been shown to be valid. In studies of medication use, for example, validation of self-report can come from examining pharmacy dispensation records or deploying electronic counters to medications as objective measures to validate a person's reported use of a medication. No such efforts have gone into the development of questions about self-reported talc use.

Even more important, perhaps, is that no study has a measure that has been shown to estimate the relevant dose of talcum powder. An "application" of talcum powder has no standard definition. It is unknown how much, if any, talcum powder reported on any of the questionnaires is applied to the perineum, how much, if any, reached the vagina, nor how much, if any, reached the ovaries. The problem is especially profound in this context, because slight inaccuracies in estimating the amount used on a daily basis could significantly alter total estimated use where the history in some cases spans multiple decades. Thus, it is impossible from the studies to determine how much, if any, talcum powder was applied to the perineum, and likewise impossible to measure how much, if any, talcum powder migrated into the vagina, across the cervix, up through the uterus and eventually reached the ovaries. At best, the wide variety of non-validated measures of talcum powder use can collect hypothesis-generating data, and there is no assurance that any estimates of talc use are accurate or valid.

Below is an example of the challenges presented when a validated measure of exposure is nonexistent:

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<sup>153</sup> See generally Aday LA, Cornelius LJ. Designing and Conducting Health Surveys: A Comprehensive Guide. 3rd ed. San Francisco, CA: 2006.

<sup>154</sup> Fowler FJ Jr. Survey Research Methods. 5th ed. Thousand Oaks, CA: 2014.

<sup>155</sup> Seifert B. Validity criteria for exposure assessment methods. Sci Total Environ. 1995; 168(2):101-107.

<sup>156</sup> See McTiernan Dep. 53:18-22 ("It was not possible to determine exactly how much talcum powder product was used").

- Consider the question of whether or not consumption of milk can either cause or protect against the development of allergies. It might seem simple that one could design a survey to ask people, with and without allergies, about their past consumption of milk. A question could be: in the past 12 months, did you drink milk? People with and without allergies could be compared by whether or not they drink milk. But does the development of allergy depend on the amount of fat in the milk? In that case, we need to ask if the milk was whole milk, skim milk, 1%, or 2% fat? And does the person only drink one of those types of milk or multiple types of milk? Perhaps a person drinks 2% milk, but uses half-and-half in their coffee. So, we would need questions to understand that. In case people change their milk preferences over time, we might need questions to determine at what ages the person drank whole milk, for example, and then when did they start also drinking skim milk.
- But what if the issue of allergy is related to protein in milk? Then we need to be able to assess any other beverages and foods that contain milk protein. We cannot simply ask about milk. The range of foods with milk protein is tremendous and includes yogurt, milkshakes, and breads. Among breads alone, milk protein can be found in loaves of bread, biscuits, donuts, crackers, pancakes, waffles, French toast and others. Milk protein can be found in other foods, too, such as cereals and desserts, including cake, cookies, pudding, ice cream and pastries. Milk protein may be in scrambled eggs, butter, cream and margarine, salad dressing and even some “non-dairy” creamers. The list of foods with milk proteins goes on and on, even including meat products such as sausage, vegetables prepared *au gratin* or with butter or cream, candy including chocolate and many soups, chowders and bisques.
- It should be apparent that our simple question about milk is far more complicated than whether or not one drinks milk.
- Once we have identified all of the foods and beverages we need to ask about, we still need to determine the amount, or “dose,” of milk consumed. This step can be very difficult. If you ask about eating soup that may have milk in it, how do you quantify it? A cup or a bowl? How big is the cup? Is the cup full to the top or about 2/3 of the way up? How much milk is in a “glass” of milk? We might need some tools to use, such as food models or empty containers, to show the person telling us the amount they consumed.
- And then if we agree on a way to standardize how large is a portion of soup or milk, how do we know that people are accurately reporting when they say they typically drink 3 glasses of milk per week? The answer is: if we want to come close to knowing the truth, then we have to demonstrate the validity of the questionnaire.

The validation process is separate from the research study and typically enrolls other people for the sole purpose of determining whether and how well the questionnaire works. One method is to ask people to fill out very detailed food diaries for a few different days (in nearly real-time as they are eating and drinking, so the information is fresh) and then compare how those same people answer a question a week later about what they consumed over the past week. The extent to which the answers using the two methods are in agreement provides evidence for the validity of the survey questions. Other approaches include asking people to take pictures of what they eat to use for validation. The main point is that there is a formal process of determining the validity of survey questions that is necessary if one wants to collect high quality data and be able to approximate the truth.

Certain of plaintiffs' experts have raised related issues in their critiques of the evidence for and against dose-response.<sup>157</sup> However, these same issues of validity of the exposure measure are just as important for assessing the overall proposition of whether or not talcum powder causes ovarian cancer. For example, Dr. Smith-Bindman criticizes Gates and other cohort studies for examining any talc use (which she labels "a weak, crude predictor").<sup>158</sup> But if Dr. Smith-Bindman believes the cohort studies suffer from assessing "any" use, she should apply this criticism even-handedly to the case-control studies and meta-analyses (such as the Penninkilampi study) that did the same. And she further should have pointed out that the questionnaires that case-control studies use to assess talc use habits are often haphazardly designed and not validated. Indeed, as Dr. Smith-Bindman observes, the Terry study (which numerous plaintiffs' experts rely on heavily) reported that the prevalence of powder use by controls in the underlying studies ranged from 15 to 45 percent, which she attributes to "variation in the definition of powder use" in the underlying studies it examined.<sup>159</sup> Her point affirms concern about the validity of talc exposure assessment and that the magnitude of error could be tremendous. But cohort studies are not uniquely subject to exposure assessment problems, and it is inappropriate for plaintiffs' experts to criticize them for this reason while ignoring similar issues with case-control studies.<sup>160</sup>

Further highlighting the importance of using validated measures of exposure, Dr. Colditz described the evolution of the Nurses' Health Study and noted that "there have been continuing efforts to validate questionnaire-based exposure measures used in the study."<sup>161</sup> For example, in order to measure nutritional exposures that might be relevant to cancer and other disease risks, Dr. Colditz noted that "[a]ssessment of long term diet is necessary to relate nutrient intake to the risk of chronic diseases," and that "this is best accomplished through the use of a food-frequency questionnaire." Further, he stated that the "Nurses' Health Study investigators have devoted great attention to the development, evaluation and refinement of food-frequency questionnaires

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<sup>157</sup> Singh Rep. at 55.

<sup>158</sup> Smith-Bindman Rep. at 21.

<sup>159</sup> Smith-Bindman Rep. at 28.

<sup>160</sup> *E.g.*, Moorman Dep. 187:13-18 (criticizing Gonzales 2016).

<sup>161</sup> Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. *Nat Rev Cancer*. 2005; 5(5):388-396. ("Colditz 2005").

for epidemiological applications.” There were no such efforts employed in the NHS, nor in any other study, to develop and validate measures of talcum powder use.

Other authors have repeatedly discussed the limits of exposure measures in the epidemiologic studies. For example, in Schildkraut, the authors stated: “A recent publication of data from the WHI, which did not find an association with genital talc use and ovarian cancer, was accompanied by an editorial that emphasized the challenges in assessing the exposure to talc due to reliance on self-report. This limitation in the measurement of the exposure variables in the current study needs to be considered when interpreting our results.”<sup>162</sup> And the Berge authors noted as a limitation to their meta-analysis that “neither the definition of the exposure of interest (genital talc use) nor the strategy for adjustment for potential confounders were fully consistent across studies.”<sup>163</sup> Another limitation was the “self-reported information on the main exposure of interest, with no external validation.”<sup>164</sup> In the Langseth (2008) paper, the authors noted that “the current body of epidemiologic evidence is insufficient to establish a causal association between perineal use of talc and ovarian cancer risk,” and pointed to the “crudeness of the exposure metric used,” and that “it is important that future studies, irrespective of study design, devote some effort to better assessment of exposure.”<sup>165</sup> This “crudeness” of the exposure measure was apparent in Terry (2013) as the authors needed to define genital powder use as “any type of powder (talc, baby, deodorizing, cornstarch or unspecified/unknown)” and acknowledged that a study limitation was “differences in the wording of questions about genital powder use between studies.”<sup>166</sup> In the same vein, another author cautioned that composition of body powders varies from one brand to the next. Thus, “[d]ata from additional cohort studies would be welcome, but without details concerning the composition of the powders used by cohort members—details that many participants may not be able to provide—the results of such studies may be similarly ambiguous in their interpretation.”<sup>167</sup> Dr. Cramer, a plaintiffs’ expert in prior talc cases, similarly acknowledged that “[t]here are inherent limitations quantifying a dose-response due to a lack of metrics for how much talc is in an ‘application,’ how much enters the vagina, and how much reaches the upper genital tract where, presumably, any deleterious effect is mediated.”<sup>168</sup> Many other authors expressed similar concerns pertaining to the accuracy of exposure measurements.<sup>169</sup>

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<sup>162</sup> Schildkraut 2016 at 1416.

<sup>163</sup> Berge 2018 at 255.

<sup>164</sup> *Id.*

<sup>165</sup> Langseth 2008.

<sup>166</sup> Terry 2013 at 812, 820.

<sup>167</sup> Rosenblatt 2011.

<sup>168</sup> Cramer 2016 at 344.

<sup>169</sup> Gonzalez 2016 (“one challenge with studying talc is that the chemical formulation of talc has changed over time, and not all powders contain the mineral talc”); Cook 1997 (“it is not clear how ascertainment of perineal powder application correctly estimates actual exposure to particles in powder that may influence ovarian cancer risk”); Mills 2004 at 463 (“the lack of dose response between talc use and EOC may be explained by the inability to quantify the actual amount of talc used per application and timing of the application”); Rosenblatt 2011 (“the validity of all these studies, including ours, may be influenced by the level of non-response among cases and

In sum, without a validated measure of talcum powder use, it is impossible to correctly determine whether or not an exposure occurred or the quantity of purported exposure, making it impossible to reliably conclude that there is a causative relationship between perineal talcum powder use and ovarian cancer based on the current literature.

**E. The Epidemiological Data Do Not Demonstrate Temporality.**

The strongest evidence for temporality comes from studies that assess the exposure at one point in time, and then assess the outcome at a future time. The prospective cohort studies are the only studies in this matter that do that and thus represent the best evidence to assess temporality. As described more fully above, the cohort studies failed to show an association of ovarian cancer with talcum powder use. The case-control studies ask about past exposure, but they ask those questions at the same time that the outcome is already known. Temporality is assumed in case-control studies, though it is not a fact, as it is in cohort studies (or clinical trials). That is the reason that recall errors and recall bias are such a concern in case-control studies. Unlike prospective studies, subjects need to accurately remember and report past exposures. Recall bias occurs when people with a disease, compared to those without a disease, report different exposure histories compared to the truth. People with a disease may be more likely to recall or report exposures than those without the disease, which can inflate the apparent risk. This distortion is especially important when measured risks are low.

While it is a different concept from temporality, latency is a concept that is important to consider when evaluating temporality. Latency is the time from exposure to development of disease. When latency is known, one would want to make sure that not only did the exposure occur in the past, but that it occurred long enough ago in the past that a cancer would have time to develop. Obviously, without determining whether or not talcum powder causes ovarian cancer, it is not possible to state that there is a known latency. Nonetheless, Dr. Wolf states that the average latency period between exposure to talc and diagnosis of ovarian cancer is at least 20 years, citing two articles<sup>170,171</sup> that do not examine this issue.<sup>172</sup> Based on this theory, several experts have stated that a limitation of the cohort studies is that they were not of sufficient length to capture latency.<sup>173</sup> Obviously, without a known latency period, that concept is only speculative. Moreover, as explained above, the cohort studies have accounted for decades of talcum powder use. Thus, if women started using talcum powder at approximately 20 years

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controls, and by the potential for misclassification (differential and non-differential) of exposure status. The latter derives not just from errors in the recall of the use of genital powder, but from the fact that the presence or concentration of talc can vary from brand to brand and even within one brand of powder over time. Therefore, even when respondents are asked specifically about perineal exposure to powders that contain talc (as in our study), they may be unable to provide accurate information.”).

<sup>170</sup> Purdie DM, Bain CJ, Siskind V, et al. Ovulation and risk of epithelial ovarian cancer. *Int. J. Cancer*. 2003; 104:228-232.

<sup>171</sup> Okada F. Beyond foreign-body-induced carcinogenesis: Impact of reactive oxygen species derived from inflammatory cells in tumorigenic conversation and tumor progression. *Int. J. Cancer*. 2007; 121:2364-2372.

<sup>172</sup> Wolf Rep. at 15.

<sup>173</sup> Singh Rep. at 11, 53; McTiernan Rep. at 47.

old<sup>174</sup> and the latency period is approximately 20 years,<sup>175</sup> then both the Women's Health Initiative Study and Sister Study would account for a sufficient latency period.

**F. The Epidemiological Data Lack Coherence.**

Dr. Hill stated that the cause and effect interpretation of the data “should not seriously conflict with the generally known facts and the biology of the disease.” Dr. Hill cited the example of temporal trends in the rise in lung cancer rates while smoking was increasing. But here, there are no published studies that have demonstrated any such ecological coherence with talcum powder and ovarian cancer. Specifically, I can find no published studies that have examined trends in ovarian cancer rates in relation to trends in talcum powder use. Dr. Hill also cited, as an example of coherence, the changes of bronchial epithelial cells in smokers. But again, here there are no studies that have demonstrated histopathological differences in ovaries of talc users and non-users (nor in any tissues of the female genital tract). This fact strongly argues against coherence.

**G. No Experimental Evidence.**

There is no experimental evidence of the relationship of talcum powder use and ovarian cancer in humans, as plaintiffs' experts agree.<sup>176</sup>

**H. The Epidemiologic Data Is Not Analogous.**

A few of the experts considered analogy, although Dr. Moorman “did not weight it heavily”<sup>177</sup> and Dr. Singh found it “less significant than other viewpoints.”<sup>178</sup> They and other experts opined that talcum powder's similarity to asbestos offers an appropriate analogy,<sup>179</sup> but asbestos and talc are distinct minerals, with distinct elemental composition and morphology, and it cannot simply be assumed that epidemiological study of asbestos can be applied by analogy to the case of talc, especially in light of the fact that talc itself has been extensively studied and its epidemiological literature reports vastly different risk levels than the asbestos literature. In particular, the talc/asbestos analogy is unpersuasive because talc exposure is not associated with an increased risk of mesothelioma or lung cancer (diseases caused by asbestos), and as set forth below, it is far from clear that asbestos causes ovarian cancer. Moreover, the limited analogy arguments that plaintiffs' experts advance do not make sense. For example, Dr. Moorman compares asbestos to “asbestiform talc,” but fails to explain why her attempted analogy applies to platy talc.<sup>180</sup> Dr. Smith-Bindman similarly refers to talc's “fibrous nature,” even though platy

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<sup>174</sup> Cramer 2016 at 335.

<sup>175</sup> Wolf Rep. at 15.

<sup>176</sup> Moorman Rep. at 38; Singh Rep. at 66; Wolf Rep. at 16.

<sup>177</sup> Moorman Rep. at 38.

<sup>178</sup> Singh Rep. at 66.

<sup>179</sup> Moorman Rep. at 38; Singh Rep. at 66; Smith-Bindman Rep. at 41.

<sup>180</sup> Moorman Rep. at 38.

talc is not fibrous, and she further essentially concedes that the talc-ovarian cancer evidence is “weak[]” in making the unsupported claim that “weaker evidence” should suffice to prove causation when there is an appropriate analogy.<sup>181</sup> In short, analogy has not been established.

**I. The Evidence For A Biological Mechanism By Which Talc Could Cause Cancer Is Weak.**

Plaintiffs’ experts generally propose that talc or alleged other constituents in talcum powder (e.g., asbestos, heavy metals or fragrance chemicals) can travel from the perineum up the genital tract to the ovaries – against gravity and the downward flow of vaginal mucous and menstrual fluids.<sup>182</sup> They also suggest an alternative pathway, via inhalation and the lymphatic system.<sup>183</sup> These proposed mechanisms are speculative and unsupported by science.

**1. Studies Have Repeatedly Stated That Scientific Evidence Is Insufficient To Show Mechanisms Of Talc-Based Ovarian Carcinogenesis.**

As an initial matter, based on my review of the available epidemiologic literature, many authors of studies have made clear that the evidence is insufficient to understand any purported mechanism by which talc-based cosmetic powders could cause ovarian cancer. For example:

Penninkilampi (2018)<sup>184</sup>

- “[T]he potential mechanism by which genital talc is associated with an increased risk of ovarian cancer hence remains unclear.”
- “[U]nfortunately, the evidence remains insufficient to understand the mechanisms with any reasonable certainty.”
- “[T]here is a substantial need for further research on a potential mechanism.”

Berge (2018)<sup>185</sup>

- “[T]he biological basis and plausibility of a possible carcinogenic effect of talc on the ovaries is still not understood and remains questionable.”

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<sup>181</sup> Smith-Bindman Rep. at 41.

<sup>182</sup> Carson Rep. at 8; Kane Rep. at 4, 14; McTiernan Rep. at 8, 58-59, 66; Moorman Rep. at 32-33; Plunkett Rep. at 27-38; Singh Rep. at 18-19, 57; Singh Dep. 212:6-18; Smith-Bindman Rep. at 35; Zelikoff Rep. at 12-14.

<sup>183</sup> Carson Rep. at 8; Kane Rep. at 14; McTiernan Rep. at 58-59, 66; Moorman Rep. at 33; Plunkett Rep. at 27-28; Singh Rep. at 18-19, 57-58; Wolf Rep. at 11, 15; Zelikoff Rep. at 14-17.

<sup>184</sup> Penninkilampi 2018 at 11-12, 14.

<sup>185</sup> Berge 2018 at 255.

Cramer (2016)<sup>186</sup>

- “[U]nfortunately, no epidemiologic study of epithelial ovarian cancer and talc has taken the opportunity to determine whether talc can actually be found in tissues removed at surgery and correlated with exposure to talc.”

Terry (2013)<sup>187</sup>

- “[T]he biological plausibility for the observed association between genital powder use and ovarian cancer has been challenged because evidence for dose-response has been inconsistent.”
- “[L]ittle is known about the biologic effects of genital powder use.”
- “[M]ore work is needed to understand how genital powders may exert a carcinogenic effect, and which constituents (e.g., talc) may be involved.”

Gates (2008)<sup>188</sup>

- “The association remains controversial due to the lack of a clear dose-response with increasing frequency or duration of talc use, the possibility of confounding or other biases, and the uncertain biological mechanism.”

Merritt (2008)<sup>189</sup>

- “[T]hese results in combination with previous studies suggest that chronic inflammation is unlikely to play a major role in the development of ovarian cancer.”

Mills (2004)<sup>190</sup>

- “[R]esearch has provided little biologic or experimental evidence to support a relationship between talcum powder use and ovarian cancer risk.”

Whittemore (1988)<sup>191</sup>

- “While these findings indicate that vaginal exposure to particulates can lead to deposition on the ovaries, they do not implicate such exposure in ovarian carcinogenesis, and data relating directly to this possibility are needed.”

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<sup>186</sup> Cramer 2016 at 344.

<sup>187</sup> Terry 2013 at 819-20.

<sup>188</sup> Gates 2008 at 2437.

<sup>189</sup> Merritt 2008 at 174.

<sup>190</sup> Mills 2004 at 464.

<sup>191</sup> Whittemore 1988.

As these excerpts make clear, plaintiffs' experts' suggestion that biological plausibility is "accepted widely" based on "robust data" is simply false.<sup>192</sup>

2. Scientific Study Does Not Support The Inhalation Or Migration Theories By Which Talc Is Supposed To Reach The Ovaries.

Scientific data also fail to demonstrate a plausible mechanism by which talc or accessory particles could physically reach the ovaries from external use.

Plaintiffs' experts principally suggest that talc and asbestos particles can travel from the perineum up the genital tract to the ovaries – against gravity and the downward flow of vaginal mucous and menstrual fluids.<sup>193</sup> The results of research addressing retrograde transport have been inconclusive.<sup>194</sup> For example, one study examining the amount of talc in the ovaries of women who had undergone surgery for benign ovarian neoplasms found no correlation between the women's talc use and their talc particle counts.<sup>195</sup> Another study reviewed pathology slides from 213 ovarian tumors and found definite silicate crystals in only five patients, which may have reflected talc contamination from surgical gloves.<sup>196</sup> And as noted by IARC, while some studies of potential retrograde movement of particles in women who were about to undergo gynecological surgery for diseases or complications of the reproductive tract or organs have suggested that such transport is possible, "broad interpretations with regard to healthy women" based on these studies "may be limited."<sup>197</sup> Thus, IARC reported that, "[o]n balance, the Working Group believed that the evidence for retrograde transport of talc to the ovaries in normal women is weak."<sup>198</sup>

Relatedly, while plaintiffs' experts point out that talc particles and asbestos fibers have been found in ovarian tissue, this fact is of no scientific significance because researchers have found such particles in the ovaries of women with and without perineal talc use or other known exposures to talc or asbestos.<sup>199</sup> The Heller (1996) study found that "talc particles were observed to a similar extent with both exposed and unexposed subjects" and that particles were actually found in higher proportions among women who did not apply talc on the perineum, stating that "our results do not support a linear dose-related ovarian talc particle burden."<sup>200</sup> As this research

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<sup>192</sup> Blair Smith Rep. at 20; Moorman Rep. at 32; Singh Rep. at 65.

<sup>193</sup> Singh Dep. 212:6-18, 215:7 ("talc can migrate upwards").

<sup>194</sup> IARC Talc Monographs at 392.

<sup>195</sup> Heller 1996.

<sup>196</sup> Yaker A, Benirschke K. A ten year study of ovarian tumors. *Virchows Arch A Pathol Anat Histol.* 1975; 366(4):275-86.

<sup>197</sup> IARC Talc Monographs at 392.

<sup>198</sup> *Id.* at 411.

<sup>199</sup> Heller 1996 at 1508, 1510; Heller DS, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. *Am J Ind Med.* 1996;29(5):435-439 (noting that asbestos fibers were found in ovarian tissue of women with and without history of exposure).

<sup>200</sup> Heller 1996 at 1508, 1510.

indicates, the presence of fibers in ovarian tissue does not establish the relevant exposure pathways.

Studies have also failed to show an association between use of talc-dusted diaphragms and condoms and ovarian cancer.<sup>201</sup> Evaluating an association with the use of talc-dusted diaphragms and condoms has been deemed “the most valid method for testing the carcinogenic potential of talc” because “[b]y definition, the female reproductive tract is exposed to talc containing powders introduced by diaphragms, whereas an exposure route based on perineal dusting requires unproven assumptions about vaginal exposure.”<sup>202</sup>

Moreover, numerous studies have considered whether tubal ligation and hysterectomy – procedures that “block the environmental contamination of the ovaries” – are associated with a decreased risk of ovarian cancer generally, while others have looked at this question in perineal talc users specifically.<sup>203</sup> Although plaintiffs’ experts assert that these studies “strongly suggest that the increased risk of ovarian cancer associated with talcum powder products use is reduced or eliminated after tubal ligation or hysterectomy,”<sup>204</sup> my review of the available literature reveals that the results have been inconsistent.<sup>205</sup> In fact, the only cohort study to address this issue concluded that “no effect modification was seen by history of tubal ligation.”<sup>206</sup> And a pooled analysis of case-control studies observed similar associations for talc use in women with tubal ligation or hysterectomy regardless of whether the “exposure to genital powder applications” occurred before or after the surgery.<sup>207</sup> Several case-control studies have found a lower incidence of ovarian cancer in patients who had tubal ligation but a higher incidence in patients who had hysterectomies,<sup>208</sup> which is a puzzling result since both hysterectomy and tubal ligation should cut off the pathway through which talc could travel to the ovaries. Because tubal ligation and hysterectomy would prevent the migration of talc particles from the perineum, the

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<sup>201</sup> Hartge 1983; Fiume 2015 at 122S (“[S]tudies demonstrating that the use of talc-dusted condoms or diaphragms, which would clearly result in exposure close to the cervical opening, [have found that talc] was generally not associated with increased RR estimates for ovarian cancer.”); Muscat & Huncharek 2008 at 5-6 (describing meta-analyses showing no association between use of talc-dusted diaphragms and condoms and ovarian cancer); Penninkilampi 2018 at 42, 44 (“Talc use on diaphragms or on sanitary napkins was not individually associated with increased risk of ovarian cancer.”).

<sup>202</sup> Muscat & Huncharek 2008 at 5, 9 (“It may be argued that the overall null findings associated with talc-dusted diaphragms and condom use is more convincing evidence for a lack of a carcinogenic effect, especially given the lack of an established correlation between perineal dusting frequency and ovarian tissue talc concentrations and the lack of a consistent dose-response relationship with ovarian cancer risk.”).

<sup>203</sup> *Id.* at 7.

<sup>204</sup> Smith-Bindman Rep. at 35.

<sup>205</sup> Muscat & Huncharek 2008 at 7; Singh Rep. at 23 (admitting that the Terry pooled study found that “[a]fter excluding those with tubal ligation and hysterectomy, the results were similar. Restricting analysis to application before tubal ligation made no substantive difference.”).

<sup>206</sup> Gertig 2000 at 251.

<sup>207</sup> Terry 2013 at 817.

<sup>208</sup> Mills 2004 (finding odds ratios of 0.88 and 1.54 for tubal ligation/no tubal ligation and odds ratios of 1.79 and 1.33 for hysterectomy/no hysterectomy); Cramer 1999 at 352 (odds ratios of 0.98 and 1.80 for tubal ligation/no tubal ligation and 2.61 and 1.60 for hysterectomy/no hysterectomy).

fact that studies have not consistently shown a reduced risk associated with these surgeries undermines the premise that talc particles travel to the ovaries and cause cancer.

Finally, some of plaintiffs' experts espouse a theory that talc or accessory particles can reach the ovaries via inhalation (i.e., that women who use cosmetic talc inhale some amount of talc particles while they are applying cosmetic talc).<sup>209</sup> But I have not seen a mechanistic study that demonstrates that inhaled talc particles can reach the ovaries, and plaintiffs' experts concede there is not sufficient evidence pertaining to inhalation of talcum powder.<sup>210</sup> Furthermore, while most of the epidemiologic studies did not examine non-perineal application of talcum powder, those that assessed application to other body parts found inconsistent results. For example, although Penninkilampi found a small elevation in risk with "any non-perineal" talc use [1.24(1.01-1.51), this finding was limited by finding significant heterogeneity across the studies. In the Terry pooled analysis of more than 18,000 women, non-perineal application showed no risk [0.98(0.89-1.07)]. Likewise, the recent study by Cramer (2016) showed no association of body use of powder with ovarian cancer [0.99[0.84-1.16].

3. The Theory That Talc Can Cause Inflammation That Promotes Cancer Lacks Scientific Support.

The theory asserted by several of plaintiffs' experts that talc particles that reach the ovaries can cause inflammation leading to cancer (the "inflammation theory") also lacks support.<sup>211</sup>

First and foremost, no biological mechanism theory accounts for the fact that talc is not mutagenic or genotoxic.<sup>212</sup> This fact significantly undermines the theory that talc causes ovarian cancer, since gene mutation is widely recognized as what triggers ovarian cancer.<sup>213</sup> And Dr. Singh's assertion – without citation – that "[t]alc has also been shown to be mutagenic"<sup>214</sup> is simply incorrect, as is Dr. McTiernan's similar assertion that talc can cause genotoxicity.<sup>215</sup> In

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<sup>209</sup> McTiernan Rep. at 66; Siemiatycki Rep. at 65; Moorman Rep. at 33; Singh Rep. at 19, 57-58.

<sup>210</sup> Moorman Dep. 303:17-304:15 (stating there is not sufficient evidence to conclude that inhaled talcum powder causes ovarian cancer because there are not "epidemiologic studies that have actually looked at inhaled talcum powder in relation to ovarian cancer"); Singh Dep. 216:14-19 (agreeing that "studies of talcum powder use failed to show a statistically significant association between nongenital use of talcum powder and ovarian cancer").

<sup>211</sup> Smith-Bindman Rep. at 12; McTiernan Rep. at 8; Siemiatycki Rep. at 65; Moorman Rep. at 33-34; Singh Rep. at 19.

<sup>212</sup> Muscat & Huncharek 2008 at 9 (citing Endo-Capron S, Renier A, Janson X, et al. In vitro response of rat pleural mesothelial cells to talc samples in genotoxicity assays (sister chromatid exchanges and DNA repair). *Toxicol In Vitro*. 1993; 7(1):7-14); IARC Talc Monographs at 399.

<sup>213</sup> Mayo Clinic, Cancer (Dec. 12, 2018), <https://www.mayoclinic.org/diseases-conditions/cancer/symptoms-causes/syc-20370588>; Anand P, Kunnumakkara AB, Sundaram C, et al. Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res*. 2008; 25(9):2097-2116, 2098 (noting that "all cancers are a result of multiple mutations").

<sup>214</sup> Singh Rep. at 19.

<sup>215</sup> McTiernan Rep. at 67.

this vein, animal studies (including studies directly injecting talc into the ovaries of rats) have not shown that prolonged exposure to talc causes ovarian cancer or precancerous changes in ovarian cells.<sup>216</sup> Likewise, in vitro and pathological studies have not shown evidence of talc-induced ovarian cancer.<sup>217</sup>

The inflammation theory is also unsupported and implausible. A recent study sought to determine whether histological signs of inflammation were associated with ovarian cancer and found “no significant correlation . . . between serous carcinoma and histological signs of inflammation or chronic tubal injury.”<sup>218</sup> Studies have not established a causal association between the use of cosmetic talc and cancers in vaginal, uterine and cervical tissue.<sup>219</sup> If talc (or alleged asbestos in talc products) produced inflammatory responses or carcinogenesis in ovarian tissue, it might also produce the same in other tissue. These tissues are closer to the perineum than the ovaries and likely are exposed to greater concentrations of talc than the ovaries.

The lack of evidence showing a reduced risk associated with the use of anti-inflammatory drugs further undermines the inflammation theory. Most meta-analyses examining this issue have found no risk reduction with either aspirin or NSAID use.<sup>220</sup> One did report a modest risk reduction for aspirin use but found no such reduction for non-steroidal anti-inflammatory drug (“NSAID”) use.<sup>221</sup> The meta-analysis concluded that “[f]urther biological and pharmacological

<sup>216</sup> Muscat & Huncharek 2008 at 9 (lifetime whole body exposure experiments in female laboratory rats found that ovarian tissue was not contaminated with talc and that ovarian tumor incidence was not increased) (citing Boorman GA, Seely JC. The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. *Regul Toxicol Pharmacol.* 1995; 21(2):242-243); Hamilton TC, Fox H, Buckley CH, et al. Effects of talc on the rat ovary. *Br J Exp Pathol.* 1984; 65(1):101-106 (study exposing rat ovaries to talc finding that the “epithelium covering the papillae was regular with no evidence of cytoplasmic or nuclear atypia”; there was no “evidence of frank neoplasia”; and that observed inflammation was not near the papillae).

<sup>217</sup> Muscat & Huncharek 2008 at 9; IARC Talc Monographs at 397-98; Lee P, Sun L, Lim CK, et al. Selective apoptosis of lung cancer cells with talc. *Eur Respir J.* 2010; 35(2):450-452, 452; Nasreen N, Mohammed KA, Brown S, et al. Talc mediates angiostasis in malignant pleural effusions via endostatin induction. *Eur Respir J.* 2007; 29(4):761-769, 761-762 (in vitro studies reporting that talc stops new blood vessels from forming and causes cell death only in malignant cells, leaving healthy cells alone).

<sup>218</sup> Malmberg K, Klynning C, Flöter-Rådestad A, Carlson JW. Serous tubal intraepithelial carcinoma, chronic fallopian tube injury, and serous carcinoma development. *Virchows Arch.* 2016; 468(6):707-713.

<sup>219</sup> Singh Dep. 209:9-16.

<sup>220</sup> Bonovas S, Filioussi K, Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. *Br J Clin Pharmacol.* 2005; 60(2):194-203 (RR 0.93 (95% CI: 0.81-1.06) for aspirin use; RR 0.88 (95% CI: 0.76-1.01) for NSAID use); Ni X, Ma J, Zhao Y, et al. Meta-analysis on the association between non-steroidal anti-inflammatory drug use and ovarian cancer. *Br J Clin Pharmacol.* 2013; 75(1):26-35 (RR 0.94 (95% CI: 0.87-1.01) for aspirin use; RR 0.89 (95% CI: 0.74-1.08) for NSAID use); Baandrup L, Faber MT, Christensen J, et al. Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. *Acta Obstet Gynecol Scand.* 2013; 92(3):245-255 (RR 0.93 (95% CI: 0.84-1.02) for aspirin use; RR 0.94 (95% CI: 0.84-1.06) for NSAID use).

<sup>221</sup> Trabert B, Ness RB, Lo-Ciganic WH, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. *J Natl Cancer Inst.* 2014; 106(2):djt431, 5 (2014) (for aspirin, OR 0.91 (95% CI: 0.84-0.99); for NSAIDs, OR 0.90 (95% CI: 0.77-1.05)).

research is necessary to understand the mechanisms of ovarian cancer risk reduction by aspirin use.”<sup>222</sup> The authors reported the results of further study just this year, continuing to find a modest decrease in risk with daily aspirin use but not with other types of anti-inflammatories, and further contradicting the inflammation theory, “observ[ing] a consistently elevated ovarian cancer risk with frequent, long-duration use of aspirin and nonaspirin NSAIDs.”<sup>223</sup> Moreover, the Wu 2009 study – on which plaintiffs’ experts have relied on the issue of dose-response – likewise found the opposite effect, reporting that, “contrary to the study hypothesis that NSAIDs may have chemopreventative effects by decreasing inflammation, we found that the risk of ovarian cancer *increased* significantly with increasing frequency and duration of NSAIDs use.”<sup>224</sup> And Merritt (2008) additionally found risk reduction with the use of anti-inflammatories, concluding that “on balance, chronic inflammation does not play a major role in the development of ovarian cancer.”<sup>225</sup> In sum, and as plaintiffs’ experts agree, studies of the effect of anti-inflammatory drugs on ovarian cancer are mixed at best, and some even show the reverse relationship – i.e., increased incidence of ovarian cancer with increased use of NSAIDs.<sup>226</sup>

Finally, “inflammation” is a broad term and does not inevitably lead to cancer. For example, pollen can lead to increased inflammation in the asthmatic lung, but it does not cause cancer. Thus, even if one finds inflammation in tissue, that does not mean that cancer inevitably or even likely follows from that. And if talc in fact caused cancer by causing inflammation, it would surely do so in patients who undergo pleurodesis (which entails the therapeutic injection of talc into the pleural cavity to cause beneficial scarring). Yet, there is no evidence that pleurodesis patients subsequently develop cancer as a result of the procedure. Plaintiffs’ expert Dr. Ghassan Saed has performed experiments – apparently for litigation purposes<sup>227</sup> – to attempt to establish an inflammation-based mechanism by which talc could cause ovarian cancer. While I leave a detailed assessment of Dr. Saed’s efforts to other experts, I did review Dr. Saed’s report and his two depositions and was struck by the irregularities in his study, which render his results highly questionable. I also read the highly skeptical comments from the reviewers at *Gynecologic Oncology*, which rejected his manuscript.<sup>228</sup> But even accepting the results of Dr. Saed’s study, they at best raise questions about the inflammation hypothesis that would have to be addressed through future *in vitro* and *in vivo* testing, as he effectively acknowledged at his

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<sup>222</sup> *Id.*

<sup>223</sup> Trabert B, Poole EM, White E, et al. Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium, *J. Nat’l Cancer Inst.* 2019; 111(2):137-145, 139-142 (emphasis added).

<sup>224</sup> Wu 2009 (emphasis added).

<sup>225</sup> Merritt 2008.

<sup>226</sup> Singh Dep. 231:23-233:2 (“[NSAIDs] don’t consistently reduce the risk of ovarian cancer”); Kane Rep. at 9-13 (“[S]ome studies show[] a protective effect of anti-inflammatory drugs on the risk of developing carcinoma, although some studies have failed to show a protective effect.”); Blair Smith Rep. at 17-18 (describing studies that “looked at the effects of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) on the risk of developing cancer” as “inconsistent”).

<sup>227</sup> Saed Dep. Vol. I 62:16-63:7, 72:10-73:2, 178:14-21.

<sup>228</sup> *Gynecologic Oncology* Email dated Sept. 19, 2018 re: GYN-18-1020: Final Decision.

deposition.<sup>229</sup>

**VII. THE ASBESTOS LITERATURE DOES NOT SUPPORT THE THEORY THAT ASBESTOS ALLEGED TO BE IN COSMETIC TALC COULD CAUSE OVARIAN CANCER.**

There are numerous problems with plaintiffs' experts' theory that asbestos is an accessory mineral present in cosmetic talc that causes ovarian cancer.

First, all of the problems addressed above with respect to plaintiffs' theories by which particulates in talcum powder could migrate to the ovaries would apply to asbestos fibers. And plaintiffs' experts' inhalation theories are all the more infirm with respect to asbestos particularly. Assuming talc contained asbestos, the larger burden of any inhaled asbestos should be seen in the lungs, which are directly exposed, rather than the ovaries, which would only be indirectly exposed, if at all. If that is the case, as Dr. Moorman testified, we should be seeing an epidemic of mesothelioma and lung cancer cases among cosmetic talc users.<sup>230</sup> But no expert has identified any studies showing that mesothelioma or lung cancer is a risk of talc use, and I am not aware of any such studies. To the contrary, studies that have looked at talc miners and millers – who would presumably confront greater exposures to asbestos if it were present in talc given the occupational context – have not found any increased incidence of mesothelioma or lung cancer attributable to talc exposure in the mines or mills.<sup>231</sup> Notably, IARC emphasized this point, stating that there was “little or inconsistent evidence of an increased risk of cancer in the studies of workers occupationally exposed to talc,” where the potential for talc inhalation would be particularly significant, and that “studies of talc miners and millers were considered to provide the best source of evidence.”<sup>232</sup> And the body of literature investigating perineal talc use has focused on ovarian cancer, and not mesothelioma or lung cancer, which indicates that researchers have not even considered them worth investigating.

In addition to the lack of a plausible mechanism by which asbestos could reach the ovaries, there is also a lack of any reliable epidemiology supporting such a causal connection. There have been relatively few studies examining the association between asbestos exposure and

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<sup>229</sup> Saed Dep. Vol. II 542:16-25.

<sup>230</sup> Moorman Dep. 112:7-15 (“Q. You would agree with me that if talcum powder, that is used in cosmetic talc products, is, in fact, contaminated with asbestos, then you would expect to see increased cancer incidence rates, for example, of mesothelioma, in cosmetic talc miners and millers; correct? . . . [A] I wouldn’t be surprised to see that, yes.”).

<sup>231</sup> Fiume 2015 at 119S (studies looking at occupational inhalational talc exposure do not show an increased risk of lung disease); Pira PE, Coggiola M, Ciocan C, et al. Mortality of Talc Miners and Millers from Val Chisone, Northern Italy: An Updated Cohort Study. *J Occup Environ Med.* 2017; 59(7):659-664 (concluding that there was a lack of association between exposure to asbestos-free talc, lung cancer, and mesothelioma in a cohort of talc miners and millers from Val Chisone, Italy); Wergeland E, Andersen A, Baerheim A. Morbidity and mortality in talc-exposed workers. *Am J Ind Med.* 1990; 17(4):505-513 (finding no elevated incidence of lung cancer or mesothelioma in a cohort of 94 talc miners and 295 talc millers).

<sup>232</sup> IARC Talc Monographs at 412.

ovarian cancer.<sup>233</sup> Of the studies that have reported a statistically significant association between asbestos exposure and ovarian cancer, all looked at populations heavily exposed to asbestos in the workplace.<sup>234</sup> As noted by the authors of a 2011 meta-analysis that included most of this research, studies examining the asbestos-ovarian cancer association have been “limited,” in part due to a “[s]mall number of cases” – i.e., “[m]uch fewer women than men have been exposed to asbestos, particularly in [the] more heavily exposed occupational settings” that have predominantly been examined.<sup>235</sup> Although some of these studies show a statistically significant elevated risk, others do not, and the overall results are highly inconsistent.<sup>236</sup> Moreover, the meta-analysis calculated an overall standardized mortality ratio (“SMR”) of 1.75 across 16 studies, which is not even a doubling of risk.<sup>237</sup> The SMR in these studies ranged from 0.79 in a study of Polish women diagnosed with asbestosis (in which there was only one case of ovarian cancer across 490 exposed women) to 4.77 in a study of Italian women compensated for asbestosis (nine cases of ovarian cancer in 631 exposed women).<sup>238</sup> Ten of the 16 studies reported SMRs lower than 2.0, none of them statistically significant.<sup>239</sup>

<sup>233</sup> International Agency for Research on Cancer, Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 100C: Asbestos (Chrysotile, Amosite, Crocidolite, Tremolite, Actinolite, and Anthophyllite) 253 (2012) (“IARC Asbestos Monographs”) (observing that “the published literature examining the association between asbestos exposure and cancer of the ovaries is relatively sparse”).

<sup>234</sup> Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. *Br J Ind Med.* 1982; 39(4):344-348 (for gas mask workers exposed to crocidolite, SMR 2.75 (95% CI: 1.42-4.81)); Berry G, Newhouse ML, Wagner JC. Mortality from all cancers of asbestos factory workers in east London 1933-80. *Occup Environ Med.* 2000; 57(11):782-785 (for insulation workers, SMR 2.53 (95% CI: 1.16-4.80)); Camargo MC, Stayner LT, Straif K. Occupational exposure to asbestos and ovarian cancer: a meta-analysis. *Environ Health Perspect.* 2011; 119(9):1211-1217, 1216 (“Camargo 2011”) (meta-analysis “restricted to highly exposed women” reporting “findings . . . consistent with the hypothesis that exposure to asbestos is associated with an increased risk of ovarian cancer”); Germani D, Belli S, Bruno C, et al. Cohort mortality study of women compensated for asbestosis in Italy. *Am J Ind Med.* 1999; 36(1):129-134 (“Germani 1999”) (for cement works, SMR 5.40 (95% CI: 1.75-12.61); for textile works, SMR 5.26 (95% CI: 1.43-13.47); for all workers, SMR 4.77 (95% CI: 2.18-9.06)); IARC Asbestos Monographs at 256 (concluding that there is a causal association based “on five strongly positive cohort mortality studies of women with *heavy occupational exposure* to asbestos”) (emphasis added); Magnani C, Ferrante D, Barone-Adesi F, et al. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occup Environ Med.* 2008; 65(3):164-170 (for cement factory workers, SMR 2.27 (95% CI: 1.04-4.32)); Wignall BK, Fox AJ. Mortality of female gas mask assemblers. *Br J Ind Med.* 1982; 39(1):34-38. (“Wignall & Fox 1982”) (for gas mask workers, SMR 2.13).

<sup>235</sup> Reid A, de Klerk N, Musk AW. Does exposure to asbestos cause ovarian cancer? A systematic literature review and meta-analysis. *Cancer Epidemiol Biomarkers Prev.* 2011; 20(7):1287-129, 1287 (“Reid 2011”).

<sup>236</sup> *See id.* (“The relationship between asbestos exposure and ovarian cancer is not as well understood.”); *see also id.* at 1293 fig. 1 (chart showing the 16 studies, 12 of which did not report statistically significant results); *id.* at 1294 (“The present study has shown that 4 of 14 cohort studies reported a statistically significant excess rate for ovarian cancer among women exposed to asbestos. Of the remaining 10 studies, 5 reported a tendency to excess but failed to reach statistical significance and 5 reported rates that were similar to those of their reference populations. Strong evidence of consistency was not observed among these studies, although no study reported any protective effect.”); IARC Asbestos Monographs at 254-56 (describing cohort studies and case-control studies).

<sup>237</sup> Reid 2011 at 1287 (abstract).

<sup>238</sup> *Id.* at 1289.

<sup>239</sup> *Id.* at 1289-90.

Addressing this body of research, the authors of the 2011 meta-analysis noted above acknowledged an IARC Working Group's recent conclusion that a causal association between asbestos exposure and ovarian cancer had been established,<sup>240</sup> but criticized that conclusion as "premature and not wholly supported by the evidence."<sup>241</sup> The authors also emphasized that "[s]trong evidence of consistency was not observed among these studies,"<sup>242</sup> pointing out that "no significant excess risk was reported among those studies that examined the incidence of ovarian cancer where cases were ascertained from a cancer registry" as opposed to from death certificates, which is significant because there is evidence of misclassification in death certificates.<sup>243</sup> The authors also noted that many studies involved too few women to address dose-response.<sup>244</sup> With respect to the studies that did address dose-response, the findings "were inconsistent"; no study showed a "statistically significant trend of ovarian cancer with degree of asbestos exposure"; and "there was no evidence of a significant trend across studies as grouped exposure increased."<sup>245</sup> In light of these conclusions, I find it puzzling that some of plaintiffs' experts claim reliance on this meta-analysis for the conclusion that "[a]sbestos has been established as a cause of . . . epithelial ovarian cancer."<sup>246</sup> The study itself claims the opposite.

In addition, no study has found that asbestos exposure comparable to that allegedly sustained by women who use cosmetic talc causes an increased risk of ovarian cancer. Specifically, the occupational studies described above include workers who worked with raw asbestos as part of their job for months or years at a time.<sup>247</sup> And as Dr. Moorman testified, the level of exposure is qualitatively different in the occupational context from the exposure to the genital areas alleged by plaintiffs.<sup>248</sup> I am not aware of any study showing that the use of cosmetic talc would result in asbestos exposures comparable to occupational asbestos exposure even if the cosmetic talc contained trace amounts of asbestos, as claimed by plaintiffs' experts. Thus, the results of occupational studies cannot be reliably extrapolated to exposure scenarios such as cosmetic talc use.

The results of the occupational asbestos studies also cannot be used to support causation of ovarian cancer in cosmetic talc users because the studies have predominantly examined exposure to crocidolite asbestos or some combination of crocidolite and chrysotile, and

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<sup>240</sup> IARC Asbestos Monographs at 256.

<sup>241</sup> Reid 2011 at 1294.

<sup>242</sup> *Id.*

<sup>243</sup> *Id.* at 1293-94.

<sup>244</sup> *Id.* at 1294.

<sup>245</sup> *Id.*

<sup>246</sup> McTiernan Rep. at 57; McTiernan Dep. 268:21-25; Moorman Dep. 108:6-109:10, 111:7-14.

<sup>247</sup> Germani 1999 at 129 ("Subjects included in this cohort were certainly exposed to high levels of asbestos."); Wignall & Fox 1982 at 35 (subjects were "directly exposed to asbestos dust," and "by the end of the working day they were covered in fluff from the pads" they worked on).

<sup>248</sup> Moorman Dep. 106:4-17.

crocidolite is regarded as the most potent form of asbestos.<sup>249</sup> I note that studies examining the composition of talc-based body powders have not observed crocidolite fibers.<sup>250</sup>

Even assuming exposure to asbestos of some variety and in certain exposure scenarios can cause ovarian cancer, no science supports the notion – put forth by a number of plaintiffs’ experts – that “any exposure” to asbestos can cause ovarian cancer.<sup>251</sup> To the contrary, as suggested by the discussion of occupational studies above, the available data suggest that very significant exposure would be necessary. This conclusion is strongly supported by the fact that the few studies that have looked at environmental asbestos exposure (in women living in an asbestos mining town and family members of male asbestos factory workers) rather than occupational exposure do not show a statistically significant increased rate of ovarian cancer or increased mortality from ovarian cancer.<sup>252</sup> For example, in one study of women who lived near or worked in a crocidolite mine and who had cumulative exposures of up to 40 fiber/cc-years, there was no increased risk of ovarian cancer.<sup>253</sup> Even these studies are not perfectly analogous to the asbestos exposure alleged through perineal use of cosmetic talc. But they underscore the fact that not every circumstance where there is asbestos exposure, even crocidolite exposure, leads to elevated ovarian cancer risk.

Finally, I note that studies addressing whether there is an association between asbestos and ovarian cancer have cautioned that to the extent there is an observed association, it may be inflated by the misclassification of other diseases such as mesothelioma as ovarian cancer on subjects’ death certificates.<sup>254</sup> As these studies have explained, it has only recently become

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<sup>249</sup> Reid 2011 at 1291 (noting that crocidolite is “the most mesotheliogenic of the asbestos fibers”); IARC Asbestos Monographs at 242 (discussing studies finding no excess mortality for cancer of the pharynx in amosite asbestos miners but an excess mortality rate for crocidolite miners and a higher risk rate for factory workers exposed to crocidolite than workers exposed to chrysotile); *id.* at 254-55 (relying on studies that involved crocidolite and, in some cases also chrysotile).

<sup>250</sup> IARC Talc Monographs at 303-05.

<sup>251</sup> *E.g.*, Moorman Dep. 75:22-76:3.

<sup>252</sup> Reid A, Heyworth J, de Klerk NH, Musk B. Cancer Incidence Among Women and Girls Environmentally and Occupationally Exposed to Blue Asbestos at Wittenoom, Western Australia. *Int J Cancer*. 2008; 122(10):2337-2344 (study of 2,552 women living in an asbestos mining town in Australia (reporting a “minimum estimate” standard incidence ratio (“SIR”) of 1.11 (95% CI 0.39-1.84) and “maximum estimate” SIR of 1.43 (95% CI 0.50-2.37), depending on the method used to determine when to stop following women in the study; a standard incidence ratio reports the ratio of the number of cases of cancer found in the studied population relative to the expected number of such cases as derived from broader population statistics rather than a control group, and a standard mortality ratio (“SMR”) employs a similar comparison but focuses on rates of death rather than incidence of disease); Reid A, Segal A, Heyworth JS, et al. Gynecologic and breast cancers in women after exposure to blue asbestos at Wittenoom. *Cancer Epidemiol Biomarkers Prev*. 2009; 18(1):140-147 (“Reid 2009”) (analysis of ovarian cancer incidence in the same population (SIR 1.18 (95% CI: 0.45-1.91))); Ferrante D, Bertolotti M, Todesco A, et al. Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. *Environ Health Perspect*. 2007; 115(10):1401-1405 (study of family members of men employed at an asbestos-cement factory in Italy (SMR 1.42 (95% CI: 0.71-2.54))).

<sup>253</sup> Reid 2009.

<sup>254</sup> Reid 2011 at 1287 (explaining that many studies ascertained mortality from death certificates, “[t]he accuracy of [which] has been questioned repeatedly”; observing that it has been “particularly difficult to distinguish

technologically possible to reliably “distinguish pathologically between peritoneal mesothelioma and ovarian cancer.”<sup>255</sup> As the authors of one meta-analysis explained, even a low number of misclassification errors can drastically affect reported mortality rates given the limited number of ovarian cancer cases in the studies.<sup>256</sup> Notably, the authors of that meta-analysis did not find a statistically significant ovarian cancer incidence when looking only at studies that obtained ovarian cancer diagnoses from cancer registries rather than death certificates.<sup>257</sup>

### **VIII. HEALTH CANADA AND THE ANALYSIS BY MOHAMED TAHER**

I understand that plaintiffs’ experts have begun relying on the recent draft screening assessment of talc by Health Canada<sup>258</sup> and the related analysis by Mohamed Taher<sup>259</sup> and others. I have reviewed these documents, and they are consistent with the opinions I set forth above and do not support a conclusion that talc causes ovarian cancer.

The Health Canada (“HC”) assessment raises a number of new issues that if anything further cloud the scientific picture and erect further obstacles to a conclusion that perineal talcum powder use causes ovarian cancer. For example, the document highlights other sources of exposure to talc. Specifically, it states that “a potential concern for human health has been identified” for perineal exposure to talc “from use of various self-care products (e.g., body powder, baby powder, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs).”<sup>260</sup> The document further notes that talc is present in approximately 8,500 self-care products, in addition to being found as a food additive, in medications, and many other consumer and commercial products.<sup>261</sup>

In other respects, the HC assessment largely covers old ground. Indeed, as part of the overall assessment, there was a health effects assessment that relied on the work of other

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between peritoneal mesothelioma and ovarian serous carcinoma”). Notably, this meta-analysis found that “no significant excess risk was reported among those studies that examined the incidence of ovarian cancer where cases [were] ascertained from a cancer registry.” *Id.* at 1294.

<sup>255</sup> Camargo 2011 at 1216; *see id.* at 1215 (observing that earlier meta-analyses concluded that they could not conclude causality despite evidence of an association because of concerns about tumor misclassification and failure to account for known risk factors).

<sup>256</sup> Reid 2011 at 1294 (“Where disease outcome was identified from the cause of death as listed on the death certificate, given the small numbers of ovarian cancer cases in each study, even misclassification of 1 cancer may exert a large impact on the exposure effect.”).

<sup>257</sup> *Id.* (“The meta-analysis of those studies that examined ovarian cancer as determined on the death certificate reported an excess risk. In contrast, no significant excess risk was reported among those studies that examined the incidence of ovarian cancer where cases [were] ascertained from a cancer registry.”).

<sup>258</sup> *See* Health Canada, Draft screening assessment talc (Mg<sub>3</sub>H<sub>2</sub>(SiO<sub>3</sub>)<sub>4</sub>), Chemical Abstracts Service Registry Number 14807-96-6, <https://www.canada.ca/content/dam/eccc/documents/pdf/pded/talc/Draft-screening-assessment-talc.pdf> (“HC Assessment”).

<sup>259</sup> Taher 2018.

<sup>260</sup> *See* HC Assessment at iii.

<sup>261</sup> *See id.* at 6.

agencies (e.g., IARC and the United States Environmental Protection Agency) and a literature search. With regard to perineal exposure to talc, the HC assessment cites IARC's Group 2B classification (possibly carcinogenic to humans), and the CIR Expert Panel (2013) that "determined that there is no causative relationship between cosmetic use of talc in the perineal area and ovarian cancer[.]"<sup>262</sup> The assessment notes that rodents are poor experimental models for perineal studies and that "animal data are very limited."<sup>263</sup> In terms of human studies, it cites several meta-analyses, including those cited by plaintiffs' experts, as well a newer unpublished manuscript by Taher (2018).<sup>264</sup>

In a discussion of mode of action, the HC assessment states that "the etiology of most ovarian tumors, in general, has not been well established."<sup>265</sup> While it notes that talc particles instilled into the uterus or to a lesser extent the vagina can be found in the ovaries of rats, no similar translocation occurred in studies of rabbits and monkeys.<sup>266</sup>

The HC assessment found no health effects of ingested talc or dermally applied talc. With regard to inhalation, it cites the Danish EPA (2016) "note that talc is not absorbed via inhalation."<sup>267</sup> It points to potential for retention of talc in the lungs as leading to talc-induced pneumoconiosis or talcosis in certain industrial settings.<sup>268</sup> The assessment considers the NTP rat study of inhalation (1993) of talc with doses as high as 18 mg/m<sup>3</sup>.<sup>269</sup> It cites conclusions of a symposium of experts from the NTP as well as academic, industry and government experts who evaluated the NTP study results and reached a consensus that because the dose was so high, the neoplasms seen were not relevant to human health risk assessment.<sup>270</sup> The lung tumors seen in only female rats were judged to be attributed to the general particle effects of dust, and not specific to talc, and the pheochromocytomas were attributed to tissue hypoxia, and not talc per se.<sup>271</sup>

The HC assessment also addresses the issue of asbestos, noting that selective mining, ore processing, and benefaction can remove many of the impurities from mined talc, that United States Pharmacopeia ("USP") requires the absence of asbestos, and that cosmetic grade talc should comply with USP standards.<sup>272</sup> Further, "health effect studies on cosmetic-grade talc

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<sup>262</sup> *Id.* at 15.

<sup>263</sup> *Id.*

<sup>264</sup> *Id.* at 16-17.

<sup>265</sup> *Id.* at 18.

<sup>266</sup> *Id.* at 18-19.

<sup>267</sup> *Id.* at 11.

<sup>268</sup> *Id.*

<sup>269</sup> *Id.* at 12.

<sup>270</sup> *Id.* at 13.

<sup>271</sup> *Id.*

<sup>272</sup> *Id.* at 3.

cited in this assessment were considered to be free of asbestos.”<sup>273</sup>

At the end of the day, the HC assessment failed to conclude that talc use causes ovarian cancer,<sup>274</sup> and plaintiffs’ experts misread the report to the extent they contend that it did.<sup>275</sup>

HC’s overall assessment appears to rely heavily on the unpublished meta-analysis by Taher and cites Taher’s Bradford Hill analysis extensively. HC’s extensive reliance on Taher is unusual and problematic. First, the manuscript has not gone through the peer-review process for publication. There is no way to know, at this point, whether and where it will ultimately be published, but even if it is, there is no assurance that the findings and conclusions will be the same once reviewers and editors have provided feedback. Second, it seems unusual to rely on the Taher paper in that there is no novelty and the studies reviewed in it have been repeatedly evaluated by other authors, whose results have, in fact, been through the peer-review process.

As a rationale for performing the study, Taher et al. cite “increasing concern that perineal exposure to talc, a commonly used personal care product, might be associated with an increased risk of ovarian cancer.”<sup>276</sup> Further, they note that “the data describing this association is somewhat inconsistent.”<sup>277</sup> Again, it is not clear why another meta-analysis of the same underlying data would be expected to solve past inconsistency.

In reviewing animal studies, Taher et al. note that “data from the animal studies [that] considered various routes of talc administration are inconsistent. . . .”<sup>278</sup> They cite the NTP rat study (1993), findings that HC stated “were not relevant to human health risk assessment” and were not specific to talc.<sup>279</sup> Taher et al. use the NTP study as evidence that, “overall, the available [sic] experimental data suggest irritation, followed by oxidative stress and inflammation, may play be involved [sic] in local carcinogenic effects of talc in the ovaries.”<sup>280</sup> Taher et al. note that “data on talc migration in the genital tract of animals is inconsistent, but could not exclude such possibility.”<sup>281</sup>

The Hill analysis performed by Taher et al. also has serious flaws. With respect to strength of association, the authors note that 6 of 30 studies showed statistically significant risk

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<sup>273</sup>

*Id.*

<sup>274</sup>

*Id.* at 28 (concluding that talc use is a “potential concern for human health”).

<sup>275</sup>

Moorman Dep. 145:19-21.

<sup>276</sup>

Taher 2018 at 2.

<sup>277</sup>

*Id.* at 3.

<sup>278</sup>

*Id.* at 22.

<sup>279</sup>

HC Assessment at 3.

<sup>280</sup>

Taher 2018 at 23.

<sup>281</sup>

*Id.* at 24.

of 1.5 or greater and that none of the cohort studies found statistically significant associations.<sup>282</sup> While these findings show marked inconsistency, they are not supportive of a strong association.

With regard to consistency, Taher et al. cite 15 of 30 studies with positive, significant associations.<sup>283</sup> Obviously, the same number do not show such an association, which is further evidence against consistency.

As to temporality, Taher et al. state that “the participants recalled that exposure to talc preceded the reported outcome,”<sup>284</sup> which ignores the fact that this recall is retrospective rather than prospective.

Regarding biologic gradient, the cited evidence is that 6 of 12 studies showed a significant dose-response trend,<sup>285</sup> which is again evidence of the inconsistency of the study findings, and is in any event wrong given that the cited positive studies included several that did not find a dose response with cumulative use, such as Mills 2004 and Rosenblatt 2011. Moreover, at a later point in the paper, the authors acknowledge that “conflicting findings were reported on the nature of the exposure-response relationship” and that a possible increasing trend is hampered by “a high degree of uncertainty surrounding many of the risk estimates.”<sup>286</sup>

For experimentation, there are no cited human studies and no tests of animal models of perineal talc and ovarian cancer. The authors again cite the NTP rat study,<sup>287</sup> which remains problematic for the reasons discussed previously.

The analysis of analogy relies on supposed similarities of talc and asbestos and the belief that there are histologic similarities of ovarian cancer and mesothelioma, and that these purported similarities have some bearing on talc causing cancer (even though Taher et al. state that “talc is not genotoxic”).<sup>288</sup>

In the discussion, the authors note subgroup differences they observed by ethnicity, menopausal state, and tubal ligation. But they go on to note that these three subgroup analyses (ethnicity, menopausal state and pelvic surgery) showed considerable heterogeneity that “might have had an impact on the results.”<sup>289</sup>

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<sup>282</sup> *Id.* at 25.

<sup>283</sup> *Id.*

<sup>284</sup> *Id.* at 26.

<sup>285</sup> *Id.*

<sup>286</sup> *Id.* at 37.

<sup>287</sup> *Id.* at 26.

<sup>288</sup> *Id.* at 27.

<sup>289</sup> *Id.* at 30.

Taher et al. reaffirmed the effect of study design on results, with, once again, positive findings only in population-based case-control studies, but not in those with hospital-based controls [0.96 (0.78-1.17)] or in cohort studies [1.06 (0.9-1.25)]. They also highlighted previously demonstrated paradoxical findings, such as lower risk of cancer with longer use of talc and the “expected, yet non-significant, negative association” with talc applied to diaphragms.<sup>290</sup> While they noted a protective effect of tubal ligation [0.64 (0.45-0.92)], they acknowledged incoherent findings of no significant effect of hysterectomy [0.89 (0.54-1.46)] and a small, non-significant higher risk in women with both tubal ligation and hysterectomy [1.06 (0.78-1.42)].<sup>291</sup>

In the conclusion, the authors state that their evaluation is consistent with that of IARC in 2010 and that it “indicates that perineal exposure to talc powder is a possible cause of ovarian cancer in humans.”<sup>292</sup> In other words, eight years later their conclusion is the same – that the evidence shows only that it is possible, not probable, that perineal talc use causes ovarian cancer. Thus, Taher does not add anything new to the body of literature addressed in this report.

## **IX. CONCLUSION**

It is my opinion, based on my qualifications and my extensive review of the available epidemiology studies and scientific literature, that there is not sufficient evidence to conclude that there is a causal relationship between perineal talcum powder exposure and ovarian cancer. The epidemiologic literature shows a non-existent association or, at most, a small association between perineal talc use and ovarian cancer that constitutes only weak epidemiologic evidence that can be attributed to bias, confounding or chance. The studies are inconsistent across study designs and within study designs, as cohort and hospital-based case-control studies do not show a statistically significant association and only a subset of the population-based case-control studies demonstrate a statistically significant association. Moreover, the case-control studies do not show any consistent evidence of a dose-response relationship, and there is a complete lack of evidence for dose-response in the cohort studies. The theories pertaining to biological plausibility are entirely speculative and have not been demonstrated in the epidemiology studies or scientific literature; rather, relevant science contradicts the purported theories of talcum powder transport and development of ovarian cancer by inflammation. Finally, the assertion that asbestos present in talc – even if true – causes ovarian cancer is problematic on the grounds that there is a lack of a plausible mechanism by which asbestos could reach the ovaries and also a lack of any reliable epidemiology supporting such a causal connection.

All of the opinions in this report are stated to a reasonable degree of scientific certainty.

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<sup>290</sup> *Id.* at 32.

<sup>291</sup> *Id.* at 33.

<sup>292</sup> *Id.* at 49.

# APPENDIX A

**Appendix A: Sample Of Pre-2014 News Articles Addressing Posited Link Between Talc Use And Ovarian Cancer**

- [1] Boston Globe, Study links talc use to ovarian cancer (Aug. 6, 1982)
- [2] New York Times, Talcum company calls study on cancer link inconclusive (August 12, 1982) (“A major talcum powder manufacturer, while criticizing a recent study linking the use of talcum powder by women to ovarian cancer, said it would further investigate any possible relationship between cosmetic-grade talc and the development of disease.”)
- [3] New York Times, Personal Health, (July 03, 1985) (“A number of studies have indicated that exposure to talc, the principal ingredient in talcum powder, increases the risk. This may be because talc is usually contaminated with particles of asbestos, which are known cancer-promoting substances.”)
- [4] Washington Post, Fighting Ovarian Cancer: Doctors Don’t Know Who’s at Risk, or Why (May 30, 1989) (“One theory is that asbestos containing talc may account for some of the increased rate of disease in western countries that emphasize personal hygiene.”)
- [5] San Francisco Chronicle, Use powder with caution (July 31, 1990)
- [6] Business Times, Safe Newways option to looking beautiful (Feb 17, 1991) (“According to him, the talc in talcum powder and colour cosmetics have a similar molecular structure as asbestos which can cause ovarian cancer while the alcohol content in mouthwash can cause throat and stomach cancer.”)
- [7] Philadelphia Inquirer, Cancer risk and talcum linked; for women who used talc for a lifetime, the risk increased 300% (July 1, 1992)
- [8] Houston Chronicle, Use of talc on panties tied to cancer (July 1, 1992)
- [9] Los Angeles Daily News, Study says talc use increases women’s risk of ovarian cancer (July 1, 1992)
- [10] Seattle Times, Study links talcum use, ovarian cancer (July 1, 1992)
- [11] St. Louis Post-Dispatch, Talcum powder, ovarian cancer linked (July 2, 1992)
- [12] The Independent, Condom talc risks, (Mar. 21, 1995) (“They point out that if it gets into the female reproductive tract, talc may result in fallopian tube fibrosis and infertility, and it may also be linked to ovarian cancer.”)
- [13] Philadelphia Inquirer, Breaking the silence: women take on a deadly stalker ovarian cancer will kill more than 14,000 this year. Activists are targeting ignorance and complacency (May 18, 1997) (“using talcum powder on the genital area, among other factors, increase the risk”)
- [14] Chicago Tribune, Survivor speaks out on ovarian cancer (Aug. 22, 1997) (“It is more prevalent in women who have had no pregnancies, have taken fertility drugs, had an early menopause, eaten a high-fat diet or frequently used talcum powder in the genital area.”)
- [15] Harvard Women’s Health Watch, Ovarian cancer (Oct. 1998) (“Several studies also suggest that two other practices -- a high-fat diet and long-term use of talcum powder on the genital region -- increase the likelihood of ovarian cancer. Researchers theorize that talc travels into the vagina, cervix, uterus, and ultimately to the ovaries, where it may prompt cellular changes and, later, cancer.”)
- [16] Chicago Tribune, Talcum takes a tumble (July 14, 1999)

**Appendix A: Sample Of Pre-2014 News Articles Addressing Posited Link Between Talc Use And Ovarian Cancer**

[17] HealthCommunities.com, Ovarian Cancer Risk Factors, (August 14, 1999) (“Some research indicates that there is an increased risk of ovarian cancer among women who apply talcum powder to the genital area or sanitary napkins.”)

[18] Cleveland Plain Dealer, Possible link between talcum powder, ovarian cancer (Aug. 17, 1999)

[19] CNN.com, Ovarian cancer: It’s less common than you think (Sept. 3, 1999) (“The ruling on talcum powder is still unclear, as well. In the past, talcum powder was sometimes contaminated with asbestos, a known cancer-causing mineral.”)

[20] Chicago Tribune, How much do you know about ovarian cancer? (Sept. 15, 1999) (“Some research has shown a possible link between talcum powders used in the genital region and an increased risk of ovarian cancer.”)

[21] Las Vegas Review Journal, Some promising treatments being developed for ovarian cancer (Nov. 25, 1999) (“In support of this, scientists point to several studies showing that talcum powder, which some women put on diaphragms or on genital skin, can raise ovarian cancer risk.”)

[22] Philadelphia Inquirer, Don’t worry about talc in eye shadow, face powder (Jan. 16, 2000) (“That doesn’t mean not to use eyeshadow or face powder with talc, but it absolutely means to consider never using it on your children, or vaginally on yourself.”)

[23] St. Louis Dispatch, Can genital warts cause cancer? (Apr. 26, 2000) (“Talc, the main ingredient of talcum powder, has been linked to ovarian cancer when used as a vaginal dusting powder.”)

[24] USA Today, Estrogen may join carcinogen list (Dec. 8, 2000) (“Research suggests that talcum powder used in feminine hygiene increases the risk of ovarian cancer.”)

[25] New York Post, Feds eye new causes of cancer (Dec. 9, 2000) (“Meanwhile, talc has been linked to an increased risk of ovarian cancer in women who use it for feminine hygiene”)

[26] Los Angeles Times, Study Suggests Aspirin May Help Prevent Ovarian Cancer (Mar. 12, 2001) (“Ovarian cancer might be preceded by inflammation due to pelvic inflammatory disease or the use of talcum powder, both of which are linked to an increased risk of the disease.”)

[27] The Guardian, Is your beauty regime damaging your health? Once again, studies are suggesting that chemicals used in cosmetics such as talc could increase the risk of cancer. Just how worried should we be . . . (Sept. 11, 2007)

[28] National Health Service, Talcum powder and ovarian cancer (Sept. 29, 2008) (“Although this study has shortcomings and does not provide strong evidence of a causal link in itself, when put in context with other studies on this topic, it adds to the body of evidence suggesting that use of talc may be linked to ovarian cancer.”)

[29] Washington Post, Cellphones are possible cancer risk, WHO says (June 1, 2011) (“Other substances that the group has categorized as ‘possibly carcinogenic’ include talcum powder, which has been possibly linked to ovarian cancer).

**Appendix A: Sample Of Pre-2014 News Articles Addressing Posited Link Between Talc Use And Ovarian Cancer**

[30] Cancer Weekly, Researchers from Pennsylvania State University Detail New Studies and Findings in the Area of Ovarian Cancer (Nov. 8, 2011) (“A number of observational studies (largely case-control) conducted over the last two decades suggest an association between use of talc powders on the female perineum and increased risk of ovarian cancer”)

[31] Women’s Health Weekly, Recent findings from University of Queensland highlight research in ovarian cancer (Apr. 5, 2012) (“Use of talcum powder in the perineal area has been associated with an increased risk of ovarian cancer”)

[32] The Guardian, Ovarian cancer: a call to arms: Susan Gubar was when she was diagnosed with ovarian cancer. It wasn't exactly tragedy - her daughters fully grown, her work complete. The tragedy is the ignorance which still surrounds this neglected disease (Sept. 1, 2012) (“Asbestos exposure, talcum powder, hormone replacement therapy, and fallout from nuclear testing have all been linked to ovarian cancer”)

[33] Huffington Post, Health Myths: 7 medical misconceptions exposed (May 16, 2013) (“Harvard researchers recently found that postmenopausal women who use talcum powder in their genital area just once a week increase their risk of developing endometrial cancer by 24 percent. Another Harvard study found a strong link between talcum powder use and ovarian cancer (it can increase the risk of developing the cancer by up to 40 percent.”)

[34] Daily Mail, Women who regularly use talcum powder increase their risk of ovarian cancer by 24% (June 18, 2013) (The researchers analysed data from 8,525 women diagnosed with ovarian cancer and compared talcum powder use with that of 9,800 women who remained cancer-free. The results, published in the journal Cancer Prevention Research, showed regularly applying the powder particles after bathing or showering raised the risk of an ovarian tumour by 24 per cent.”)

[35] Daily Mail (UK), Talc can raise ovarian cancer risk by quarter (June 19, 2013)

[36] The Sydney Morning Herald, Surprising cancer causes, (Aug. 02, 2013) (“Researchers have found a link between frequent use of talcum powder “for intimate personal hygiene” and ovarian cancer. The results published in the journal Cancer Prevention Research showed regularly applying the powder particles after bathing or showering raised the risk of an ovarian tumour by 24 per cent.”)

[37] Rapid City Journal, South Dakota jury ties talc powder to cancer risk (Oct. 05, 2013) (“A federal jury in Sioux Falls has found that a woman's use of Johnson & Johnson products that contained talcum contributed to her ovarian cancer.”)

[38] Reuters Legal, Johnson & Johnson failed to warn of possible talc-cancer link: jury (Oct. 8, 2013)

# **APPENDIX B**

**Materials Reviewed and Considered by Dr. Gregory Diette, M.D., M.H.S.**

**Expert References**

Expert Report of Michael M. Crowley, Ph.D., Nov. 12, 2018 (MDL No. 2328)

Expert Report of William E. Longo, Ph.D, and Mark W. Rigler, Ph.D., Nov. 14, 2018

Expert Report of Sarah E. Kane, M.D., Nov. 15, 2018 (MDL No. 2738)

Expert Report of Rebecca Smith-Bindman, M.D., Nov. 15, 2019 (MDL No. 2738)

Expert Report of Alan Campion, Ph.D., Nov. 16, 2018 (MDL No. 2738)

Expert Report of Arch Carson, M.D., Ph.D., Nov. 16, 2018 (MDL No. 2738)

Expert Report of Daniel L. Clarke-Pearson, M.D., Nov. 16, 2018 (MDL No. 2738)

Expert Report of Robert B. Cook, Ph.D., Nov. 16, 2018 (MDL No. 2738)

Expert Report of David Kessler, M.D., Nov. 16, 2018 (MDL No. 2738)

Expert Report of Mark Krekeler, Ph.D., Nov. 16, 2018 (MDL No. 2738)

Expert Report of Shawn Levy, Ph.D., Nov. 16, 2018 (MDL No. 2738)

Expert Report of Anne McTiernan, M.D., Ph.D., Nov. 16, 2019 (MDL No. 2738)

Expert Report of Patricia Moorman, M.S.P.H., Ph.D., Nov. 16, 2018 (MDL No. 2738)

Expert Report of Laura Plunkett , Ph.D., D.A.B.T., Nov. 16, 2018 (MDL No. 2738)

Expert Report of Ghassan Saed, Ph.D., Nov. 16, 2018 (MDL No. 2738)

Expert Report of Sonal Singh, M.D., M.P.H., Nov. 16, 2018 (MDL No. 2738)

Expert Report of Jack Siemiatycki, M.Sc., Ph.D., Nov. 16, 2018 (MDL No. 2738)

Expert Report of Ellen Blair Smith, Nov. 16, 2018 (MDL No. 2738)

Expert Report of Judith Wolf, M.D., Nov. 16, 2018 (MDL No. 2738)

Expert Report of April Zambelli-Weiner, Ph.D., M.P.H., Nov. 16, 2018 (MDL No. 2738)

Expert Report of Judith Zelikoff, Ph.D., Nov. 16, 2018 (MDL No. 2738)

Deposition of Sonal Singh, M.D., M.P.H., Jan. 16, 2019 (MDL No. 2738)

Deposition of Anne McTiernan, Jan. 28, 2019 (MDL No. 2738)

Deposition of Patricia Moorman, M.S.P.H., Ph.D. Jan. 25, 2019 (MDL No. 2738)

**Materials Reviewed and Considered by Dr. Gregory Diette, M.D., M.H.S.**

Deposition of Ghassan Saed, Ph.D., Jan. 23, 2019 (MDL No. 2738)

Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738)

Deposition of Jack Siemiatycki, Jan. 31, 2019 (MDL No. 2738)

Deposition of Rebecca Smith-Bindman, M.D., Feb. 7, 2019 (MDL No. 2738)

Deposition of Rebecca Smith-Bindman, M.D., Feb. 8, 2019 (MDL No. 2738)

Deposition of April Zambelli-Weiner, Ph.D., Jan. 11, 2019 (MDL No. 2738)

Deposition of April Zambelli-Weiner, Ph.D., Feb. 7, 2019 (MDL No. 2738)

Gynecologic Oncology Email dated Sept. 19, 2018 re: GYN-18-1020: Final Decision (Ex. 35 to the Deposition of Ghassan Saed, Ph.D., Feb. 14, 2019 (MDL No. 2738))

**Scholarly References**

Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. *Br J Ind Med.* 1982; 39(4):344-348

Aday LA, Cornelius LJ. *Designing and Conducting Health Surveys: A Comprehensive Guide.* 3rd ed. San Francisco, CA: 2006

Alberg AJ, Moorman PG, Crankshaw S, et al. Socioeconomic Status in Relation to the Risk of Ovarian Cancer in African-American Women: A Population-Based Case-Control Study. *Am J Epidemiol.* 2016; 184(4):274-283

Anand P, Kunnumakkara AB, Sundaram C, et al. Cancer is a preventable disease that requires major lifestyle changes. *Pharm Res.* 2008; 25(9):2097-2116

Andrade C. Understanding Relative Risk, Odds Ratio, and Related Terms. *J Clin Psychiatry.* 2015; 76(7):e857-861

Baandrup L, Faber MT, Christensen J, et al. Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. *Acta Obstet Gynecol Scand.* 2013; 92(3):245-255

Berge W, Mundt K, Luu H, Boffetta P. Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis. *Eur J Cancer Prev.* 2018; 27(3):248-257

Berry G, Newhouse ML, Wagner JC. Mortality from all cancers of asbestos factory workers in east London 1933-80. *Occup Environ Med.* 2000; 57(11):782-785

Boorman GA, Seely JC. The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. *Regul Toxicol Pharmacol.* 1995; 21(2):242-243.

**Materials Reviewed and Considered by Dr. Gregory Diette, M.D., M.H.S.**

Bonovas S, Filioussi K, Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. *Br J Clin Pharmacol*. 2005; 60(2):194-203

Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. *Br J Cancer*. 1989; 60(4):592-598

Camargo MC, Stayner LT, Straif K. Occupational exposure to asbestos and ovarian cancer: a meta-analysis. *Environ Health Perspect*. 2011; 119(9):1211-1217

Chang S, Risch HA. Perineal Talc Exposure and Risk of Ovarian Carcinoma. *Cancer*. 1997; 79(12):2396-2401

Chen Y, Wu PC, Lang JH, et al. Risk factors for epithelial ovarian cancer in Beijing, China. *Int J Epidemiol*. 1992; 21(1):23-29

Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA*. 2003; 289(24):3243-3253

Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. *Nat Rev Cancer*. 2005; 5(5):388-396

Cook LS, Kamb ML, Weiss NS. Perineal Powder Exposure and the Risk of Ovarian Cancer *Am J Epidemiol*. 1997; 145(5):459-465

Cramer DW, Liberman RF, Titus-Ernstoff L, et al. Genital Talc Exposure and Risk of Ovarian Cancer. *Int J Cancer*. 1999; 81(3):351-356

Cramer DW, Titus-Ernstoff L, McKolanis JR, et al. Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2005; 14(5):1125-1131

Cramer DW, Vitonis AF, Terry KL, et al. The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States. *Epidemiology*. 2016; 27(3):334-346

Cramer DW, Welch WR, Berkowitz RS, Godleski JJ, Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. *Obstet Gynecol*. 2007; 110(2 Pt 2):498-501

Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: a case-control study. *Cancer*. 1982; 50(2):372-376

Cramer DW, Xu H. Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. *Ann Epidemiol*. 1995; 5(4):310-314

Elwood JM. Causal Relationships in Medicine: A Practical System for Critical Appraisal. Oxford: 1988, 163-182

**Materials Reviewed and Considered by Dr. Gregory Diette, M.D., M.H.S.**

Endo-Capron S, Renier A, Janson X, et al. In vitro response of rat pleural mesothelial cells to talc samples in genotoxicity assays (sister chromatid exchanges and DNA repair). *Toxicol In Vitro*. 1993; 7(1):7-14

Ferrante D, Bertolotti M, Todesco A, et al. Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. *Environ Health Perspect*. 2007; 115(10):1401-1405

Fiume MM, Boyer I, Bergfeld WF, et al. Safety Assessment of Talc as Used in Cosmetics. *Int J Toxicol*. 2015; 34(1 Suppl):66S-129S

Fowler FJ Jr. *Survey Research Methods*. 5th ed. Thousand Oaks, CA: 2014

Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype. *Am J Epidemiol*. 2010; 171(1):45-53

Gates MA, Tworoger SS, Terry KL, et al. Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 2008; 17(9):2436-2444

Germani D, Belli S, Bruno C, et al. Cohort mortality study of women compensated for asbestosis in Italy. *Am J Ind Med*. 1999; 36(1):129-134

Gertig DM, Hunter DJ, Cramer DW, et al. Prospective Study of Talc Use and Ovarian Cancer. *J Natl Cancer Inst*. 2000; 92(3): 249-252

Godard B, Foulkes WD, Provencher D, et al. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *Am J Obstet Gynecol*. 1998; 179(2):403-410

Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR. Douching, Talc Use, and Risk of Ovarian Cancer. *Epidemiology*. 2016; 27(6): 797-802

Gordis L. *Epidemiology*. 5th ed. Philadelphia, PA: 2014

Green A, Purdie D, Bain C, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. *Int J Cancer*. 1997; 71(6):948-951

Hamilton TC, Fox H, Buckley CH, et al. Effects of talc on the rat ovary. *Br J Exp Pathol*. 1984; 65(1):101-106

Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. *Obstet Gynecol*. 1992; 80(1):19-26

Harlow BL, Weiss NS. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *Am J Epidemiol*. 1989; 130(2):390-394

**Materials Reviewed and Considered by Dr. Gregory Diette, M.D., M.H.S.**

Hartge P, Hoover R, Leshner LP, McGowan L. Talc and Ovarian Cancer. JAMA. 1983; 250(14):1844

Hartge P, Stewart P. Occupation and ovarian cancer: a case-control study in the Washington, DC, metropolitan area, 1978-1981. J Occup Med. 1994; 36(8):924-927

Health Canada, Draft screening assessment talc ( $\text{Mg}_3\text{H}_2(\text{SiO}_3)_4$ ), Chemical Abstracts Service Registry Number 14807-96-6, <https://www.canada.ca/content/dam/eccc/documents/pdf/pded/talc/Draft-screening-assessment-talc.pdf>

Health Canada, Risk management scope for talc ( $\text{Mg}_3\text{H}_2(\text{SiO}_3)_4$ ), Chemical Abstracts Service Registry Number 14807-96-6, 2018.

Heller DS, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. Am J Ind Med. 1996; 29(5):435-439.

Heller DS, Westhoff C, Gordon RE, Katz N. The Relationship Between Perineal Cosmetic Talc Usage and Ovarian Talc Particle Burden. Am J Obstet Gynecol. 1996; 174(5):1507-1510

Hill AB. The Environment and Disease: Association or Causation? Proc R Soc Med. 1965; 58(5):295-300

Houghton SC, Reeves KW, Hankinson SE, et al. Perineal Powder Use and Risk of Ovarian Cancer. J Natl Cancer Inst. 2014; 106(9): dju208

Huncharek M, Geschwind JF, Kupelnick B. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. Anticancer Res. 2003; 23(2C):1955-1960

International Agency for Research on Cancer, Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 100C: Asbestos (Chrysotile, Amosite, Crocidolite, Tremolite, Actinolite, and Anthophyllite) 253 (2012)

International Agency for Research on Cancer, Monographs on the Evaluation of Carcinogenic Risks to Humans Vol. 93: Carbon Black, Titanium Dioxide, and Talc 18-19 (2010)

Jordan SJ, Green AC, Whiteman DC, Webb PM, Australian Ovarian Cancer Study Group. Risk factors for benign, borderline and invasive mucinous ovarian tumors: epidemiological evidence of a neoplastic continuum? Gynecol Oncol. 2007; 107(2):223-230

Jordan SJ, Green AC, Whiteman DC, Webb PM. Risk factors for benign serous and mucinous epithelial ovarian tumors. Obstet Gynecol. 2007; 109(3):647-654

Kotsopoulos J, Terry KL, Poole EM, et al. Ovarian cancer risk factors by tumor dominance, a surrogate for cell of origin. Int J Cancer. 2013; 133(3):730-739

**Materials Reviewed and Considered by Dr. Gregory Diette, M.D., M.H.S.**

Kurta ML, Moysich KB, Weissfeld JL, et al. Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. *Cancer Epidemiol Biomarkers Prev.* 2012; 21(8):1282-1292

Langseth H, Hankinson SE, Siemiatycki J, Weiderpass E. Perineal Use of Talc and Risk of Ovarian Cancer. *J Epidemiol Community Health.* 2008; 62(4):358-360

Lee P, Sun L, Lim CK, et al. Selective apoptosis of lung cancer cells with talc. *Eur Respir J.* 2010; 35(2):450-452

Letter from Food & Drug Administration, U.S. Department of Health and Human Services, to Samuel S. Epstein, M.D., Cancer Prevention Coalition, University of Illinois (Apr. 1, 2014)

Magnani C, Ferrante D, Barone-Adesi F, et al. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occup Environ Med.* 2008; 65(3):164-170

Malmberg K, Klynning C, Flöter-Rådestad A, Carlson JW. Serous tubal intraepithelial carcinoma, chronic fallopian tube injury, and serous carcinoma development. *Virchows Arch.* 2016; 468(6):707-713

Mayo Clinic, Cancer (Dec. 12, 2018), <https://www.mayoclinic.org/diseases-conditions/cancer/symptoms-causes/syc-20370588>

Merritt MA, Green AC, Nagle CM, et al. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer.* 2008; 122(1):170-176

Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *Int J Cancer.* 2004; 112(3):458-464

Moorman PG, Palmieri RT, Akushevich L, et al. Ovarian cancer risk factors in African-American and white women. *Am J Epidemiol.* 2009; 170(5):598-606

Muscat JE, Huncharek MS. Perineal talc use and ovarian cancer: a critical review. *Eur J Cancer Prev.* 2008; 17(2):139-146

Nasreen N, Mohammed KA, Brown S, et al. Talc mediates angiostasis in malignant pleural effusions via endostatin induction. *Eur Respir J.* 2007; 29(4):761-769

National Cancer Institute, NCI Dictionary of Cancer Terms, “hazard ratio,” <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/hazard-ratio>.

National Cancer Institute, Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ®)—Health Professional Version, <https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq> (last updated Jan. 4, 2019)

Ness RB, Grisso JA, Cottreau C, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology.* 2000; 11(2):111-117

**Materials Reviewed and Considered by Dr. Gregory Diette, M.D., M.H.S.**

Ni X, Ma J, Zhao Y, et al. Meta-analysis on the association between non-steroidal anti-inflammatory drug use and ovarian cancer. *Br J Clin Pharmacol*. 2013; 75(1):26-35

Okada, F. Beyond foreign-body-induced carcinogenesis: Impact of reactive oxygen species derived from inflammatory cells in tumorigenic conversation and tumor progression. *Int. J. Cancer*. 2007; 121:2364-2372.

Penninkilampi R, Eslick GD. Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. *Epidemiology*. 2018; 29(1):41-49

Peres LC, Risch H, Terry KL, et al. Racial/ethnic differences in the epidemiology of ovarian cancer: a pooled analysis of 12 case-control studies. *Int J Epidemiol*. 2018; 47(2):460-472

Purdie DM, Bain CJ, Siskind V, et al. Ovulation and risk of epithelial ovarian cancer. *Int. J. Cancer*. 2003; 104:228-232.

Pira PE, Coggiola M, Ciocan C, et al. Mortality of Talc Miners and Millers from Val Chisone, Northern Italy: An Updated Cohort Study. *J Occup Environ Med*. 2017; 59(7):659-664

Purdie D, Green A, Bain C, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. *Int J Cancer*. 1995; 62(6):678-684

Reid A, de Klerk N, Musk AW. Does exposure to asbestos cause ovarian cancer? A systematic literature review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2011; 20(7):1287-1295

Reid A, Heyworth J, de Klerk NH, Musk B. Cancer Incidence Among Women and Girls Environmentally and Occupationally Exposed to Blue Asbestos at Wittenoom, Western Australia. *Int J Cancer*. 2008; 122(10):2337-2344

Reid A, Segal A, Heyworth JS, et al. Gynecologic and breast cancers in women after exposure to blue asbestos at Wittenoom. *Cancer Epidemiol Biomarkers Prev*. 2009; 18(1):140-147

Rosenblatt KA, Szklo M, Rosenshein NB. Mineral fiber exposure and the development of ovarian cancer. *Gynecol Oncol*. 1992; 45(1):20-25

Rosenblatt KA, Weiss NS, Cushing-Haugen KL. Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes Control*. 2011; 22(5):737-742

Rothman KJ, Pastides H, Samet J. Interpretation of Epidemiologic Studies on Talc and Ovarian Cancer 4 (Nov. 28, 2000), <https://ntp.niehs.nih.gov/ntp/newhomeroc/roc12/mcewen-07-14-04.pdf>

Schildkraut JM, Abbott SE, Alberg AJ, et al. Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES). *Cancer Epidemiol Biomarkers Prev*. 2016; 25(10):1411-1417

**Materials Reviewed and Considered by Dr. Gregory Diette, M.D., M.H.S.**

Seifert, B. Validity criteria for exposure assessment methods. *The Science of the Total Environment*. 1995; 168: 101-107.

Taher MK, Farhat N, Karyakina NA, et al. Systematic Review and Meta-Analysis of the Association Between Perineal Use of Talc and Risk of Ovarian Cancer (2018) (unpublished manuscript)

TalcDataResults-janehall.xlsx

Terry KL, Karageorgi S, Shvetsov YB, et al. Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls. *Cancer Prev Res (Phila)*. 2013; 6(8):811-821

Trabert B, Ness RB, Lo-Ciganic WH, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. *J Natl Cancer Inst*. 2014; 106(2):djt431

Trabert B, Poole EM, White E, et al. Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium. *J Natl Cancer Inst*. 2019; 111(2):137-145

Tzonou A, Polychronopoulou A, Hsieh CC, et al. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int J Cancer*. 1993; 55(3):408-410

Wergeland E, Andersen A, Baerheim A. Morbidity and mortality in talc-exposed workers. *Am J Ind Med*. 1990; 17(4):505-513

Whittemore AS, Wu ML, Paffenbarger RS Jr, et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am J Epidemiol*. 1988; 128(6):1228-1240

Wignall BK, Fox AJ. Mortality of female gas mask assemblers. *Br J Ind Med*. 1982; 39(1):34-38

Wong C, Hempling RE, Piver MS, et al. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstet Gynecol*. 1999; 93(3):372-376

Wu AH, Pearce CL, Tseng CC, et al. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *Int J Cancer*. 2009; 124(6):1409-1415

Wu AH, Pearce CL, Tseng CC, Pike MC. African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates. *Cancer Epidemiol Biomarkers Prev*. 2015; 24(7):1094-100

Yaker A, Benirschke K. A ten year study of ovarian tumors. *Virchows Arch A Pathol Anat Histol*. 1975; 366(4):275-86

# APPENDIX C

**CURRICULUM VITAE**  
**The Johns Hopkins University School of Medicine**

June 2017

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**GREGORY B. DIETTE, MD, MHS**

**DEMOGRAPHIC AND PERSONAL INFORMATION**

**Current Appointment:**

*University:* Professor of Medicine  
Division of Pulmonary and Critical Care Medicine  
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### **Education and Training**

1981-1986	B.S.	The University of Pennsylvania Wharton School, Philadelphia, PA. BS degree in economics. Concentration: Management of Entrepreneurship
1981-1986	B.A.	The University of Pennsylvania School of Arts and Sciences Philadelphia, PA. English; Minor in Chemistry
1986-1990	M.D.	Temple University School of Medicine, Philadelphia, PA
1995-1997	M.H.S.	Johns Hopkins University, School of Hygiene and Public Health Epidemiology; Clinical Epidemiology

### **Post-Doctoral Training**

1990-1993	Intern-Resident, Department of Internal Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA
1994-1995	Clinical Fellow, Division of Pulmonary and Critical Care, Johns Hopkins University School of Medicine, Baltimore, MD
1995-1998	Research Fellow, Division of Pulmonary and Critical Care, Johns Hopkins University School of Medicine, Baltimore, MD

### **Professional Experience:**

1991-1993	Assistant Clinical Instructor, University of Pennsylvania School of Medicine, Philadelphia, PA
1993-1994	Clinical Instructor, University of Pennsylvania School of Medicine, Philadelphia, PA
1993-1994	Attending Physician, Full-time, Department of Emergency Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA
1996-1999	Senior Physician Scientist, Quality Assessment and Improvement Systems Division, Covance Health Economics and Outcomes Services. Washington, D.C.
1998-2000	Instructor, Departments of Medicine and Epidemiology, Johns Hopkins University, Baltimore, MD
1998-present	Attending Physician, Department of Medicine, Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center, Baltimore, MD Duties include outpatient practice devoted to adult asthma and general pulmonary medicine; inpatient care in acute care hospital and intensive care units.
1998-2005	Core Faculty, Program for Medical Practice and Technology Assessment, Johns Hopkins University, Baltimore, MD

- 2000-2005 Assistant Professor of Medicine, Departments of Medicine and Epidemiology, Johns Hopkins University, Baltimore, MD
- 2005-2011 Associate Professor of Medicine, Departments of Medicine and Epidemiology, Johns Hopkins University, Baltimore, MD
- 2001-2015 Director of Clinical Research, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD.
- 2011-Present Professor of Medicine, Schools of Medicine and Public Health, Johns Hopkins University, Baltimore, MD
- 2011-Present Director, Obstructive Lung Disease Program, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD

## RESEARCH ACTIVITIES

### Original Research

1. Grasso M, Weller WE, Shaffer TJ, **Diette GB**, Anderson GF. Capitation, Managed Care, and Chronic Obstructive Pulmonary Disease. *American Journal of Respiratory and Critical Care Medicine* 1998;158:133-138.
2. **Diette GB**, White P, Terry P, Jenckes M, Wise RA, Rubin H. Quality Assessment through Patient Self-Report of Symptoms Pre- and Post- Fiberoptic Bronchoscopy. *Chest* 1998;114:1446-1453.
3. **Diette GB**, Wiener CM, White P. The Higher Risk of Bleeding in Lung Transplant Recipients from Bronchoscopy is Independent of Traditional Bleeding Risks: Results of a Prospective Cohort Study. *Chest* 1999;115:397-402.
4. **Diette GB**, Wu AW, Skinner EA, Clark R, Markson L, McDonald R, Huber M, Markson L, Steinwachs D. Treatment Patterns Among Adult Asthmatics: Factors Associated with Overuse of Inhaled  $\beta$ -Agonists and Underuse of Inhaled Corticosteroids. *Archives of Internal Medicine* 1999;159: 2697-2704.
5. Barr LF, Campbell SE, **Diette GB**, Gabrielson EW, Kim S, Shim H, Dang CV. C-Myc Suppresses the Tumorigenicity of Lung Cancer Cells and Down-regulates Vascular Endothelial Growth Factor Expression. *Cancer Research* 2000; 60:143-9.
6. **Diette GB**, White P, Terry P, Jenckes M, Rosenthal D, Rubin HR. Utility of On-site Cytopathology Assessment for Bronchoscopic Evaluation of Lung Masses and Adenopathy. *Chest* 2000; 117:1186-1190.
7. Lechtzin N, Rubin HR, Jenckes M, White P, Zhou L, Thompson DA, **Diette GB**. Predictors of Pain Control in Patients Undergoing Flexible Bronchoscopy. *American Journal of Respiratory and Critical Care Medicine* 2000; 162:440-445.
8. **Diette GB**, Markson L, Skinner EA, Nguyen TTH, Algatt-Bergstrom P, Clark R, Wu AW. Nocturnal Asthma in Children Affects School Attendance, School Performance and Parents' Work Attendance. *Archives of Pediatric and Adolescent Medicine* 2000;154:923-928.

9. **Diette GB**, Skinner EA, Markson L, Algatt-Bergstrom P, Nguyen TTH, Clark RD, Wu AW. Consistency of Care with National Guidelines for Children with Asthma in Managed Care. *Journal of Pediatrics* 2001;138:59-64.
10. Lechtzin N, Wiener CM, Clawson L, Chaudhry V, **Diette GB**. Hospitalization in amyotrophic lateral sclerosis: Causes, Costs and Outcomes. *Neurology* 2001;56:753-757.
11. Krishnan JA, **Diette GB**, Skinner EA, Clark BD, Steinwachs D, Wu AW. Race and Sex Differences in Consistency of Care with National Asthma Guidelines in Managed Care Organizations. *Archives of Internal Medicine* 2001;161:1660-1668.
12. **Diette GB**, Skinner EA, Nguyen TTH, Markson L, Clark BD, Wu AW. Comparison of Quality of Care of Specialist and Generalist Physicians as Usual Source of Asthma Care for Children. *Pediatrics* 2001;108: 432-437.
13. Wu AW, Young Y, Skinner EA, **Diette GB**, Vogeli C, Huber M, Peres A, Steinwachs D. Quality of Care and Outcomes of Adult Asthmatics Treated by Specialists and Generalists in Managed Care. *Archives of Internal Medicine* 2001;161:2554-2560.
14. Rubin HR, Pronovost P, **Diette GB**. From a Process of Care to a Measure: The Development and Testing of a Quality Indicator. *International Journal for Quality in Health Care* 2001; 13: 489-496.
15. Rubin HR, Pronovost P, **Diette GB**. The advantages and disadvantages of process-based measures of health care quality. *International Journal for Quality in Health Care* 2001; 13: 469-474.
16. Lechtzin N, Wiener CM, Shade DM, Clawson L, **Diette GB**. Spirometry in the supine position improves the detection of diaphragmatic weakness in ALS. *Chest* 2002; 121: 436-442.
17. Wolfenden LL, **Diette GB**, Skinner EA, Steinwachs DM, Wu AW. Gaps in Asthma Care of the Oldest Adults. *Journal of the American Geriatrics Society* 2002; 50: 877-883.
18. **Diette GB**, Krishnan J, Dominici F, Haponik E, Skinner EA, Steinwachs D, Wu AW. Asthma in older patients: Factors associated with hospitalization. *Archives of Internal Medicine* 2002;162:1123-1132.
19. Lechtzin N, Rothstein J, **Diette GB**, Wiener CM. Amyotrophic Lateral Sclerosis: Evaluation and Treatment of Respiratory Impairment. *Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases* 2002;3:5-13.
20. Allen-Ramey FC, Clawson L, **Diette GB**, McDonald RC, Skinner EA, Steinwachs DM, Wu AW. Methods Aimed at Improving Asthma Care and Outcomes Management. *Disease Management & Health Outcomes* 2002;10(8):495-503.
21. Lechtzin N, Rubin HR, Jenckes M, White P, **Diette GB**. Patient satisfaction with bronchoscopy. *American Journal of Respiratory and Critical Care Medicine* 2002;166: 1326-1331.
22. Scatarige JD, **Diette GB**, Merriman B, Haponik EF, Fishman EK. Availability, Requesting Practices, and Barriers to Referral for High-Resolution Computed Tomography of the Lungs: Results of a Survey of U.S. Pulmonologists. *Academic Radiology* 2002;9:1370-1377.

23. Srinivasan A, Wolfenden LL, Song X, Hartsell T, Jones HD, **Diette GB**, Orens JB, Yung RC, Ross TL, Mackie K, Merz W, Scheel PJ, Haponik EF, Perl TM. An outbreak of *Pseudomonas aeruginosa* associated with flexible bronchoscopes. *New England Journal of Medicine* 2003 Jan 16;348: 221-7.
24. Wolfenden LL, **Diette GB**, Krishnan JA, Skinner EA, Steinwachs DM, Wu AW. Lower physician estimate of underlying asthma severity leads to under-treatment. *Archives of Internal Medicine* 2003; 163:231-6.
25. Scatarige JD, **Diette GB**, Merriman B, Haponik EF, Fishman EK. Utility of High-resolution CT for Management of Patients with Diffuse Lung Disease: Results of a Survey of U.S. Pulmonary Physicians. *Academic Radiology* 2003; 10:167-175.
26. Scatarige JD, **Diette GB**, Merriman B, Fishman EK. Physician Satisfaction with HRCT Services Provided by Radiologists: Results of a Nationwide Survey of American Pulmonary Sub-specialists. *American Journal of Roentgenology* 2003; 180:585-589.
27. **Diette GB**, Lechtzin N, Haponik E, Devrotes A, Rubin HR. Distraction Therapy with Nature Sights and Sounds Reduces Pain During Flexible Bronchoscopy: A Complementary Approach to Routine Analgesia. *Chest* 2003; 123(3):941-948.
28. Patil S, Krishnan JA, Lechtzin N, **Diette GB**. In-Hospital Mortality Following Acute Exacerbation of Chronic Obstructive Pulmonary Disease. *Archives of Internal Medicine* 2003 May 26;163(10): 1180-6.
29. Hehn BT, Haponik E, Rubin HR, Lechtzin N, **Diette GB**. The Relationship of Age to Process of Care and Patient Tolerance of Bronchoscopy. *Journal of the American Geriatrics Society* 2003 51:917-922.
30. Krishnan JA, Parce PB, Martinez T, **Diette GB**, Brower RG. Caloric Intake in Medical Intensive Care Unit Patients: Consistency of Care with Guidelines and Relationship to Clinical Outcomes. *Chest* 2003; 124:297-305.
31. Robinson L, Wu AW, Haponik EF, **Diette GB**. Internists' Adherence to Guidelines for Prevention of Intravascular Catheter Infections. *JAMA* 2003;290(21):2802.
32. Alberg AJ, **Diette GB**, Ford JG. Invited Commentary: Attendance and Absence as Markers of Health Status – The Example of Active and Passive Cigarette Smoking. *Am J Epidemiol* 2003; 157:870-873.
33. Lechtzin N, Wiener CM, Clawson L, Davidson MC, Anderson F, Gowda N, **Diette GB** and the ALS CARE Study Group. Use of noninvasive ventilation in patients with amyotrophic lateral sclerosis. *ALS and Other Motor Neuron Disorders* 2004;5(1):9-15.
34. Robinson L, **Diette GB**, Song X, Brower RG, Krishnan JA. Low Caloric Intake is Associated with Nosocomial Blood Stream Infections in Patients in the Medical Intensive Care Unit. *Critical Care Medicine* 2004;32(2)350-357.
35. Hansel NN, Wu AW, Chang B, **Diette GB**. Quality of Life in Tuberculosis: Patient and Provider Perspectives. *Quality of Life Research* 2004;13:639-652.

36. Yurk R, **Diette GB**, Skinner EA, Steinwachs DM, Wu AW. Predicting Patient Reported Asthma Outcomes for Adults in Managed Care. *American Journal of Managed Care* 2004;10:321-328.
37. Swartz LJ, Callahan KA, Butz AM, Rand CA, Kanchanaraksa S, **Diette GB**, Krishnan JA, Breyse PN, Buckley TJ, Mosley AM, Eggleston PA. Methods and Issues in Conducting a Community-Based Environmental Randomized Trial. *Environmental Research* 2004 June;95(2):156-65.
38. Matsui EC, Krop EJM, **Diette GB**, Aalberse RC, Smith AL, Eggleston PA. Mouse Allergen Exposure and Immunologic Responses: IgE-Mediated Mouse Sensitization, Mouse-Specific IgG and IgG4. *Annals of Allergy, Asthma and Immunology* 2004; 93(2):171-8.
39. Hansel NN, Merriman B, Haponik EF, **Diette GB**. Hospitalizations for Tuberculosis in the United States in 2000: Predictors of In-hospital Mortality. *Chest* 2004; 126(4):1079-86.
40. Okelo S, Wu AW, Krishnan J, Rand CS, Skinner EA, **Diette GB**. Emotional Quality of Life and Outcomes in Adolescents with Asthma. *Journal of Pediatrics* 2004; 145(4):523-9.
41. Chang B, Wu AW, Hansel NN, **Diette GB**. Quality of life in tuberculosis: A review of the English language literature. *Quality of Life Research* 2004; 13:1633-1642.
42. **Diette GB**, Krishnan JA, Wolfenden LL, Skinner EA, Steinwachs DM, Wu AW. Relationship of Physician Estimate of Underlying Asthma Severity to Asthma Outcomes. *Annals of Allergy, Asthma and Immunology* 2004; 93(6):546-52.
43. Huang I, **Diette GB**, Dominici F, Frangakis C, Wu AW. Variations of Physician Group Profiling Indicators for Asthma Care. *Am J Managed Care*. 2004;10:38-44.
44. Skinner EA, **Diette GB**, Algatt-Bergstrom P, Nguyen TTH, Clark B, Markson LE, Wu AW. The Asthma Therapy Assessment Questionnaire (ATAQ) for Children and Adolescents. *Disease Management*. 2004;7:305-313.
45. Huang I, Dominici F, Frangakis C, **Diette GB**, Damberg CL, Wu AW. Is risk-adjustor selection more important than statistical approach for provider profiling? Asthma as an example. *Medical Decision Making*. 2005 Jan-Feb 25(1):20-34.
46. Sapkota A, Symons JM, Kleissl J, Wang L, Parlange MB, Ondov J, Breyse PN, **Diette GB**, Eggleston PA, and Buckley TJ. Impact of the 2002 Canadian forest fires on particulate matter air quality in Baltimore city. *Environmental Science Technology* 2005 Jan 1;39(1):24-32.
47. Huang I, Frangakis C, Dominici F, **Diette GB**, Wu, AW. Application of a propensity score approach for risk adjustment in profiling multiple physician groups on asthma care. *Health Services Research*. 2005;40(1):253-278.
48. **Diette GB**, Scatarige JC, Haponik EF, Merriman B, Fishman EK. Do High-Resolution CT Findings of Usual Interstitial Pneumonitis Obviate Lung Biopsy? *Respiration*. 2005;72:134-141.
49. Breyse PN, Buckley TJ, Williams D, Beck CM, Kanchanaraksa S, Swartz LJ, Callahan KA, Butz AM, Rand CS, **Diette GB**, Krishnan JA, Moseley AM, Curtin-Brosnan J, Durkin NB, Eggleston PA.

Indoor Exposures to Air Pollutants and Allergens in the Homes of Asthmatic Children in Inner-City Baltimore. *Environmental Research*. 2005;98:167-176.

50. Hansel NN, Hilmer SC, Georas SN, Cope LM, Guo J, Irizarry RA, **Diette GB**. Oligonucleotide Microarray Analysis of Peripheral Blood Lymphocytes in Severe Asthma. *Journal of Laboratory and Clinical Medicine* 2005 May;145(5):263-274.
51. Girgis RE, Champion HC, **Diette GB**, Johns RA, Permutt S, Sylvester JT. Decreased Exhaled Nitric Oxide in Pulmonary Arterial Hypertension: Response to Bosentan Therapy. *American Journal of Respiratory and Critical Care Medicine* 2005;172(3):352-7.
52. Robinson L, Wu AW, Haponik EF, **Diette GB**. Why is it that internists do not follow guidelines for preventing intravascular catheter infections? *Infection Control Hospital Epidemiology* 2005;26(6):525-533.
53. Wanner TJ, Gerhardt SG, **Diette GB**, Orens JB. The Utility of Cytopathology Testing in Lung Transplant Recipients. *J Heart and Lung Transplant*. 2005;24(7):870-874.
54. Matsui EC, **Diette GB**, Krop EJM, Aalberse RC, Smith AL, Curtin-Brosnan J, Eggleston PA. Mouse allergen-specific immunoglobulin G and immunoglobulin G4 and allergic symptoms in immunoglobulin E-sensitized laboratory animal workers. *Clin Exp Allergy*. 2005;35:1347-1353.
55. Eggleston PA, **Diette GB**, Lipsett M, Lewis T, Tager I, McConnell R, Chrischilles R, Lanphear B, Miller R, Krishnan J. Lessons Learned for the Study of Childhood Asthma from the Centers for Children's Environmental Health and Disease Prevention Research. *Environ Health Perspect*. 2005;113(10):1430-1436.
56. Eggleston PA, Butz A, Rand C, Curtin-Brosnan J, Kanchanaraks S, Swartz L, Breyse P, Buckley T, **Diette GB**, Merriman B, Krishnan J. Home environmental intervention in inner-city asthma: a randomized controlled clinical trial. *Ann Allergy Asthma and Immunology*. 2005;95(6):496-497.
57. Weiss CR, Scatarige JC, **Diette GB**, Haponik EF, Merriman B, Fishman, EK. CT Pulmonary Angiography is the First-Line Imaging Test for Acute Pulmonary Embolism: A Survey of US Clinicians. *Academic Radiology*. 2006 Apr; 13(4):434-46.
58. Colom AJ, Teper AM, Vollmer WM, **Diette GB**. Risk Factors for the Development of Bronchiolitis Obliterans in Children with Bronchiolitis. *Thorax*. 2006 Jun; 61(6):462-3.
59. Scatarige JC, Weiss CR, **Diette GB**, Haponik EF, Merriman B, Fishman EK. Scanning Systems and Protocols used during imaging for Acute Pulmonary Embolism: How Much do our Clinical Colleagues Know? *Academic Radiology*. 2006; 13:678-685.
60. Matsui EC, **Diette GB**, Krop EJM, Aalberse RC, Smith AL, Eggleston PA. Mouse Allergen-specific Immunoglobulin G4 and risk of mouse skin test sensitivity. *Clin Exper Allergy*. 2006;36(8): 1097-103.
61. Krishnan V, **Diette GB**, Rand CS, Bilderback AL, Merriman BJ, Hansel NN, Krishnan JA. Mortality in patients hospitalized for asthma exacerbations in the United States. *Am J Resp Crit Care Med*. 2006 Jun 15;174(6):633-8.

62. Lechtzin N, John M, Irizarry R, Merlo C, **Diette GB**, Boyle MP. Outcomes of Adults with Cystic Fibrosis Infected with Antibiotic Resistant *Pseudomonas aeruginosa*. *Respiration*. 2006;73(1):27-33.
63. Hansel NN, Eggleston PA, Krishnan JA, Curtin-Brosnan J, Rand CS, Patino CM, **Diette GB**. Asthma-Related Health Status Determinants of Environmental Control Practices for Inner-City Pre-School Children. *Annals of Allergy, Asthma & Immunology*. 2006 Sep; 97(3):409-17.
64. Matsui EC, Eggleston PA, Buckley TJ, Krishnan JA, Breyse P, Rand C, **Diette GB**. Household Mouse Allergen Exposure and Asthma Morbidity in Inner-City Pre-School Children. *Annals of Allergy, Asthma & Immunology*. 2006; 97(4): 514-20.
65. Hansel NN, Rand CS, Krishnan JA, Okelo S, Breyse PN, Eggleston PA, Matsui E, Curtin-Brosnan J, **Diette GB**. Influence of Caregiver's Health Beliefs and Experiences on their Use of Environmental Control Practices in Homes of Pre-School Children with Asthma. *Pediatric Asthma, Allergy & Immunology*. 2006;19(4):231-242.
66. Matsui EC, Eggleston PA, Breyse PN, Rand CS, **Diette GB**. Mouse allergen-specific antibody responses in inner-city children with asthma. *Journal of Allergy and Clinical Immunology* 2007;119(4):910-5.
67. Schmier JK, Manjunath R, Halpern MT, Jones ML, Thompson K, **Diette GB**. The impact of inadequately controlled asthma in urban children on quality of life and productivity. *Annals of Allergy Asthma Immunology* 2007;98(3):245-251.
68. Okelo SO, Wu AW, Merriman B, Krishnan JA, **Diette GB**. Are Physician Estimates of Asthma Severity Less Accurate in Black than in White Patients? *Journal of General Internal Medicine* 2007;22(7):976-81.
69. Han MK, Kim MG, Mardon R, Renner P, Sullivan S, **Diette GB**, Martinez FJ. Spirometry utilization for COPD? How do we measure up? *Chest*. 2007;132(2):403-9.
70. **Diette GB**, Patino CM, Merriman B, Paulin L, Okelo S, Thompson K, Krishnan JA, Quartey R, Perez-Williams D, Rand C. Patient Factors that Physicians Use to Assign Asthma Treatment. *Archives of Internal Medicine*. 2007;167(13):1360-6.
71. Sharma HP, Matsui EC, Eggleston PA, Hansel NN, Curtin-Brosnan J, **Diette GB**. Does current asthma control predict future health care use among black preschool-aged inner-city children? *Pediatrics*. 2007 Nov;120(5):e1174-81.
72. **Diette GB**, Hansel NN, Buckley TJ, Curtin-Brosnan J, Eggleston PA, Matsui EC, McCormack MC, Williams DL, Breyse PN. Home indoor pollutant exposures among inner-city children with and without asthma. *Environmental Health Perspectives*. 2007 Nov;115(11):1665-9.
73. Weiss CR, **Diette GB**, Haponik EF, Merriman B, Scatarige JC, Fishman EK. Pretest risk assessment in suspected acute pulmonary embolism. *Academic Radiology*. 2008 Jan;15(1):3-14.
74. Hansel NN, Cheadle C, **Diette GB**, Wright J, Thompson KM, Barnes KC, Georas SN. Analysis of CD4+T cell gene expression in allergic subjects using two different microarray platforms. *Allergy*. 2008;63:366-369.

75. Okelo SO, Patino CM, Hansel NN, Eggleston PA, Krishnan JA, Rand CS, **Diette GB**. Use of Asthma Specialist Care in High-Risk Inner-City Black Children. *Pediatric Asthma Allergy & Immunology*. 2007;20(4):255-262.
76. Okelo SO, Patino CM, Riekert K, Merriman B, Bilderback BS, Hansel NN, Thompson K, Thompson J, Quartey R, Rand CS, **Diette GB**. Patient Factors that Pediatricians Use to Assign Asthma Treatment. *Pediatrics*, 2008;122(1):e195-201.
77. Tonorezos ES, Breyse PN, Matsui EC, McCormack MC, Curtin-Brosnan J, Williams D'Ann, Hansel NN, Eggleston PA, **Diette GB**. Does neighborhood violence lead to depression among caregivers of children with asthma? *Social Science Medicine*. 2008;67(10):31-7.
78. Hansel NN, Breyse PN, McCormack MC, Matsui EC, Curtin-Brosnan J, Williams DL, Moore JL, Cuhnan JL, **Diette GB**. A longitudinal study of indoor nitrogen dioxide levels and respiratory symptoms in inner-city children with asthma. *Environmental Health Perspectives* 2008;116(10):1428-32.
79. Kim S, Aung T, Berkeley E, **Diette GB**, Breyse P. Measurement of Nicotine in Household Dust. *Environmental Research*. 2008;108(3):289-93.
80. Curtin-Brosnan J, Matsui EC, Breyse PN, McCormack MC, Hansel NN, Tonorezos ES, Eggleston PA, Williams D'Ann, **Diette GB**. Parent Report of Pests and Pets and Indoor Allergen Levels in Inner City Homes. *Annals of Allergy, Asthma and Immunology*. 2008;101(5):517-23.
81. Patino, CM, Okelo SO, Rand CS, Riekert KA, Krishnan JA, Thompson K, Quartey RI, Perez-Williams D, Bilderback A, Merriman B, Paulin L, Hansel N, **Diette GB**. The Asthma Control and Communication Instrument: a clinical tool developed for ethnically diverse populations. *Journal of Allergy and Clinical Immunology*. 2008;122(5):936-943.e6.
82. McCormack MC, Breyse PN, Hansel NN, Matsui EC, Tonorezos E, Curtin-Brosnan J, Eggleston PA, **Diette GB**. Common Household Activities are Associated with Elevated Particulate Matter Concentrations in Bedrooms of Inner-City Baltimore Preschool Children. *Environmental Research*, 2008;106(2):148-55.
83. McCormack MC, Breyse PN, Matsui EC, Hansel NN, Williams D, Curtin-Brosnan J, Eggleston P, **Diette GB**. In-home particle concentrations and childhood asthma morbidity. *Environ Health Perspect*. 2009;117(1):294-8.
84. O'Brien Jr JM, Aberegg SK, Ali NA, **Diette GB**, Lemeshow S. Results from the National Sepsis Practice Survey: predictions about mortality and morbidity and recommendations for limitation of care orders. *Crit Care*, 2009;13(3):R96.
85. Clerisme-Beaty E, Karam S, Rand C, Patino CM, Bilderback A, Riekert KA, Okelo SO, **Diette GB**. Does higher body mass index contribute to worse asthma control in an urban population? *J Allergy Clin Immunol*, 2009;124(2):207-12.
86. Mathias RA, Grant AV, Rafaels N, Hand T, Gao L, Vergara C, Tsai YJ, Yang M, Campbell M, Foster C, Gao P, Togias A, Hansel NN, **Diette G**, Adkinson NF, Liu MC, Faruque M, Dunston GM, Watson HR, Bracken MB, Hoh J, Maul P, Maul T, Jedlicka AE, Murray T, Hetmanski JB, Ashworth R, Ongaco CM, Hetrick KN, Doheny KF, Pugh EW, Rotimi CN, Ford J, Eng C,

- Burchard EG, Sleiman PM, Hakonarson H, Forno E, Raby BA, Weiss ST, Scott AF, Kabesch M, Liang L, Abecasis G, Moffatt MF, Cookson WO, Ruczinski I, Beaty TH, Barnes KC. A genome-wide association study on African-ancestry populations for asthma. *J Allergy Clin Immunol*. 2010 Feb;125(2):336-346.e4.
87. Castro M, Rubin AS, Laviolette M, Fiterman J, De Andrade Lima M, Shah PL, Fiss E, Olivenstein R, Thomson NC, Niven RM, Pavord ID, Simoff M, Duhamel DR, McEvoy C, Barbers R, Ten Hacken NH, Wechsler ME, Holmes M, Phillips MJ, Erzurum S, Lunn W, Israel E, Jarjour N, Kraft M, Shargill NS, Quiring J, Berry SM, Cox G, and **AIR2 Trial Study Group**. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med*. 2010;181(2):116-24.
88. **Diette GB**, Sajjan SG, Skinner EA, Weiss TW, Wu A, Markson LE. Using the pediatric Asthma Therapy Assessment Questionnaire to measure asthma control and health care utilization in children. *The Patient: Patient-Centered Outcomes Research*. 2009; 2 (4), 233-241
89. **Diette GB**, Orr P, McCormack MC, Gandy W, Hamar N. Is Pharmacologic Care of COPD Consistent with Guidelines? *Population Health Manage*. 2010 Feb;13(1):21-6.
90. Breyse PN, **Diette GB**, Matsui EC, Butz AM, Hansel NH, and McCormack MC. Indoor Air Pollution and Asthma in Children. *Proceedings of the American Thoracic Society*. 2010 May (2):102-106.
91. Lechtzin N, Busse AM, Smith MT, Grossman S, Nesbitt S, **Diette GD**. A randomized trial of nature scenery and sounds vs. urban scenery and sounds to reduce pain in adults undergoing bone marrow aspirate and biopsy. *Journal Altern Complement Med* 2010 Sep (9):965-972. PMID:PMC3110836
92. O'Brien JM Jr, Aberegg SK, Ali NA, **Diette GD**, Lemeshow S. Results from the National Sepsis Practice Survey: Use of drotrecogin alfa (activated) and other therapeutic decisions. *Journal of Critical Care* 2010 25(4):658.e7-658.e15. PMID: PMC2978258
93. Murphy A, Chu JH, Xu M, Carey VJ, Lazarus R, Liu A, Szeffler SJ, Strunk R, Demuth K, Castro M, Hansel NN, **Diette GB**, Vonakis BM, Adkinson Jr, FN, Klanderman BJ, Senter-Sylvia J, Ziniti J, Lange C, Pastinen T, Raby BA. Mapping of numerous disease associated expression polymorphisms in primary peripheral blood CD4<sup>+</sup> lymphocytes. *Hum Mol Genet* 2010;19(23):4745-57. PMID: PMC2972694
94. Bollinger ME, **Diette GB**, Chang C-L, Stephenson JJ, Sajjan S, Fan T, Allen-Ramey FC. Patient characteristics and prescription fill patterns for allergic rhinitis medications, with a focus on montelukast, in a commercially-insured population. *Clinical Therapeutics* 2010 32(6):1093-1102.
95. Butz AM, Breyse P, Rand C, Curtin-Brosnan J, Eggleston P, **Diette GB**, Williams D, Bernert JT, Matsui EC. Household smoking behavior: Effects of indoor air quality and health in urban children with asthma. *Matern Child Health J* 15:460-468, 2011. PMID: PMC3113654
96. McCormack MC, Breyse PN, Matsui EC, Hansel NN, Peng RD, Curtin-Brosnan J, Williams DL, Wills-Karp M, **Diette GD**. Indoor Particulate Matter Increases Asthma Morbidity in Children with Non-Atopic and Atopic Asthma. *Ann of Allergy Asthma Immunol* 106(4):308-315, 2011. PMID: PMC3118306

97. Sharma S, Murphy A, Howrylak J, Himes B, Cho M, Chu JH, Hunninghake G, Fuhlbrigge A, Klandermann B, Ziniti J, Senter-Sylvia J, Liu A, Szeffler SJ, Strunk R, Castro M, Hansel NN, **Diette GB**, Vonakis BM, Adkinson Jr, NF, Carey VJ, Raby BA. The impact of race in epidemiologic studies of gene expression. *Genetic Epidemiology*, 2011;35(2):93-101.
98. **Diette GB**, Fuhlbrigge A, Allen-Ramey F, Hopper A, Sajjan S, Markson LE. Asthma severity in patients initiating controller monotherapy versus combination therapy. *J Asthma* 2011;48(3): 304-310.
99. Torgerson DG, Ampleford EJ, Chiu GY, Gauderman WJ, Gignoux CR, Graves PE, Himes BE, Levin AM, Mathias RA, Hancock DB, Baurley JW, Eng C, Stern DA, Celedón JC, Rafaels N, Capurso D, Conti DV, Roth LA, Soto-Quiros M, Togias A, Li X, Myers RA, Romieu I, Berg DJ, Hu D, Hansel NN, Hernandez RD, Israel E, Salam MT, Galanter J, Avila PC, Avila L, Rodriguez-Santana JR, Chapela R, Rodriguez-Cintrón W, **Diette GB**, Adkinson NF, Abel RA, Ross KD, Shi M, Faruque MU, Dunston GM, Watson HR, Mantese VJ, Ezurum SC, Liang L, Ruczinski I, Ford JG, Huntsman S, Chung KF, Vora H, Li X, Calhoun WJ, Castro M, Sienra-Monge JJ, Del Rio-Navarro B, Deichmann KA, Heinzmann A, Wenzel SE, Busse WW, Gern JE, Lemanske RF Jr, Beaty TH, Bleecker ER, Raby BA, Meyers DA, London SJ; Children's Health Study (CHS) and HARBORS study, Gilliland FD; Genetics of Asthma in Latino Americans (GALA) Study, the Study of Genes-Environment and Admixture in Latino Americans (GALA2) and the Study of African Americans, Asthma, Genes & Environments (SAGE), Burchard EG; Childhood Asthma Research and Education (CARE) Network, Martinez FD; Childhood Asthma Management Program (CAMP), Weiss ST; Study of Asthma Phenotypes and Pharmacogenomic Interactions by Race-Ethnicity (SAPPHIRE), Williams LK; Genetic Research on Asthma in the African Diaspora (GRAAD) Study, Barnes KC, Ober C, Nicolae DL. Meta-analysis of genome-wide association studies of asthma in ethnically diverse North American populations. *Nat Genet.* 2011 Jul 31;43(9):887-92. PMCID: PMC3445408
100. Mahajan AK, **Diette GB**, Hatipoglu U, Bilderback A, Ridge A, Walker Harris V, Dalapathi V, Badlani S, Lewis S, Charbeneau JT, Naureckas ET, Krishnan JA. High frequency chest wall oscillation for asthma and chronic obstructive pulmonary disease exacerbations: A randomized sham-controlled clinical trial. *Respir Res*, 2011; 12(1): 120
101. Maziqie D, **Diette GB**, Breyse PN, Matsui EC, McCormack MC, Curtin-Brosnan J, Williams D, Peng RD, Hansel NN. Predictors of airborne endotoxin concentrations in inner city homes. *Environ Res* 111(4):614-617, 2011. PMCID: PMC3085396
102. Williams DL, Breyse PN, McCormack MC, **Diette GB**, McKenzie S, Geyh AS. Airborne cow allergen, ammonia and particulate matter at homes vary with distance to industrial scale dairy operations: An exposure assessment. *Environ Health* 2011;10(1): 72. PMCID:PMC3184623.
103. Hansel NN, Matsui EC, Rusher R, McCormack MC, Curtin-Brosnan J, Peng RG, Maziqie D, Breyse PN, **Diette GB**. Predicting future asthma morbidity in preschool inner city children. *J of Asthma* 2011, 48(8):797-803. PMID: 21861602.
104. Sharma S, Murphy A, Howrylak J, Himes B, Cho MH, Chu JH, Hunninghake GM, Fuhlbrigge A, Klanderman B, Ziniti J, Senter-Sylvia J, Liu A, Szeffler SJ, Strunk R, Castro M, Hansel NN, **Diette GB**, Vonakis BM, Adkinson NF Jr, Carey VJ, Raby PA. The impact of self-identified race on epidemiologic studies of gene expression. *Genet Epidemiol* 2011;35(2)93-101.

105. Torgerson DG, Ampleford EJ, Chiu GY, Gauderman WJ, Gignoux CR, Graves PE, Himes BE, Levin AM, Mathias RA, Hancock DB, Baurley J, Eng C, Stern DA, Celedón JC, Rafaels N, Capurso D, Conti DV, Roth LA, Soto-Quiros M, Togias A, Li X, Myers RA, Romieu I, Van den Berg DJ, Hu D, Hansel NN, Hernandez RD, Israel E, Salam MT, Galanter J, Avila PC, Avila L, Rodriguez-Santana JR, Rocio Chapela V R, Rodriguez-Cintron W, **Diette GB**, Adkinson NF, Abel RA, Ross KD, Shi M, Faruque WMU, Dunston GM, Watson HR, Mantese VJ, Ezurum SC, Liang L, Ruczinski I, Ford JG, Huntsman S, Chung KF, Vora H, Li X, Calhoun WJ, Castro M, Sierra-Monge JJ, del Rio-Navarro B, Deichmann KA, Heinzmann A, Wenzel SE *et al.* Meta-analysis of genomewide association studies of asthma in ethnically diverse North American populations. *Nat Genet.* 2011 Jul 31;43(9):887-92.
106. Butz AM, Matsui EC, Breyse P, Curtin-Brosnan J, Eggleston P, **Diette G**, Williams D, Yuan J, Bernert JT, Rand C. A randomized trial of air cleaners and a health coach to improve indoor air quality for inner-city children with asthma and secondhand smoke exposure. *Arch Pediatr Adolesc Med.* 2011 Aug;165(8):741-8.
107. Davis MF, Baron P, Price LB, Williams D, Jeyaseelan S, Hambleton I, **Diette GB**, Breyse PN, McCormack MC. Dry collection and culture methods for recovery of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* from indoor home environments. *Appl Environ Microbiol.* 2012 Apr;78(7):2474-2476. PMID:PMC3306591
108. Miranda JJ, Bernabe-Ortiz a, Smeeth L, Gilman RH, Checkley; CRONICAS Cohort Study Group. Antonio Bernabé-Ortiz, Juan P Casas, George Davey Smith, Shah Ebrahim, Raúl Gamboa, Héctor H García, Robert H Gilman, Luis Huicho, Germán Málaga, J Jaime Miranda, Víctor M Montori, Liam Smeeth; Chronic Obstructive Pulmonary Disease: William Checkley, **Gregory B Diette**, Robert H Gilman, Luis Huicho, Fabiola León-Velarde, María Rivera, Robert A Wise; Training & Capacity Building: William Checkley, Héctor H García, Robert H Gilman, J Jaime Miranda, Katherine Sacksteder. CRONICAS Cohort Study :Cardiovascular Disease. *BMJ Open* 2012 Jan 11; 2(1):e000610.
109. Demissie S, Riekert KA, Eakin MN, Bilderback A, **Diette GB**, Okelo SO. How do perceptions of asthma control and severity relate to indicators of asthma status and treatment recommendations by pediatricians? *Pediatr Allergy Immunol Pulmonol.* 2012 Mar;25(1):17-23. PMID:PMC3306591
110. **Diette GB**, Accinelli RA, Balmes JR, Buist AS, Checkley W, Garbe P, Hansel NN, Kapil V, Gordon S, Lagat DK, Yip F, Mortimer K, Perez-Padilla R, Roth C, Schwaninger JM, Punturieri A, Kiley J. Obstructive lung disease and exposure to burning biomass fuel in the indoor environment. *Global Heart J* 2012;7(3)265-270.
111. Mahajan AK, **Diette GB**, Hatipoglu U, Bilderback A, Ridge A, Harris VS, Dalapathi V, Badlani S, Lewis S, Charbeneau JT, Naureckas ET, Krishnan JA. High frequency chest wall oscillation for asthma and chronic obstructive pulmonary disease exacerbations: A randomized sham-controlled clinical trial. *Respir Res.* 2011 Sept 10;12:120. PMID:PMC3179725
112. Torjusén EN, **Diette GB**, Breyse PN, Curtin-Brosnan J, Aloe C, Matsui EC. Dose-response relationships between mouse allergen exposure and asthma morbidity among urban children and adolescents. *Indoor Air.* 2013 Aug 23; (4):268-74.
113. Lin J, Matsui W, Aloe C, Peng RD, **Diette GB**, Breyse PN, Matsui EC. Relationships between Folate and inflammatory features of asthma. *J Allergy Clin Immunol.* 2012 Mar; 131(3):918-920.

114. Paulin LM, Williams D, Oberweiser C, **Diette GB**, Breyse PN, McCormack C, Matsui EC, Peng R, Metts TA, Hansel NN. Indoor air quality in central Appalachia homes impacted by wood and coal use. *J Environ Protection* 2013;4:67-71.
115. Bose S, Jun J, **Diette G**. High frequency chest wall oscillation successful in controlling refractory asthma. *J Asthma*. 2013 Mar; 50(2):219-221.
116. Okelo SO, Eakin MN, Patino CM, Teodoro AP, Bilderback AL, Thompson DA, Loiaza-Martinez A, Rand CS, Thyne S, **Diette GB**, Riekert KA. The pediatric asthma control and communication instrument asthma questionnaire: for use in diverse children of all ages. *J Allergy Clin Immunol* 2013 Jul;132(1):55-62.
117. Lu KD, Breyse PN, **Diette GB**, Curtin-Brosnan J, Aloe C, William DL, Peng RD, McCormack MC, Matsui EC. Being overweight increases susceptibility to indoor pollutants among urban children with asthma. *J Allergy Clin Immunol* 131(4):1017-1023. 2013. PMID: PMC3889705
118. McCormack M, Matsui E, **Diette GD**, Breyse P, Aloe C, Curtin-Brosnan J. Guideline-recommended fractional exhaled nitric oxide is a poor predictor of health care use among inner-city children and adolescents receiving usual asthma care. *Chest* 2013 Sep;144(3):923-9. PMID: PMC3760744
119. Jassal MS, **Diette GB**, Dowdy DW. Cost Consequence Analysis of Multimodal Interventions with Environmental Components for Pediatric Asthma in the State of Maryland. *J Asthma*. 2013;50(6):672-80.
120. Jamieson DB, Matsui EC, Belli A, McCormack MC, Peng E, Pierre-Louis S, Curtin-Brosnan J, Breyse PN, **Diette GB**, Hansel NN. Effects of Allergic Phenotype on Respiratory Symptoms and Exacerbations in Patients with COPD. *Am J Respir Crit Care Med*. 2013 Jul 15;188(2):187-92. PMID: PMC3778754
121. Hansel NN, McCormack MC, Belli A, Matsui EC, Peng RD, Aloe C, Paulin L, Williams DL, **Diette GB**. In-home air pollution is linked to respiratory morbidity in former smokers with COPD. *Am J Crit Care Med*. 2013 May 15;187(10):1085-90. PMID: PMC3734614
122. Ahluwalia SK, Peng RD, Breyse P, **Diette GD**, Curtin-Brosnan J, Aloe C, Matsui EC. Mouse allergen is the major allergen of public health relevance in Baltimore. *J Allergy Clin Immunol* 2013 Oct; 123(4):830-835. PMID: PMC3800085
123. Bose S, Breyse PN, McCormack M, Hansel NN, Rusher RR, Matsui E, Peng R, Curtin-Brosnan J, **Diette GB**. Outdoor exposure and vitamin D levels in urban children with asthma. *Nutrition J*, 2013 Jun 12;12(1):81.
124. Martin WJ 2<sup>nd</sup>, Glass RI, Araj H, Balbus J, Collins FS, Curtis S, **Diette GB**, Elwood WN, Falk H, Hibbert PL, Keown SE, Mehta S, Patrick E, Rosenbaum J, Sapkota A, Tolunay HE, Bruce NG. Household air pollution in low-and middle-income countries: health risks and research priorities. *PLoS Med*. 2013 Jun;10(6):e1001455.
125. Matsui EC, Hansel NN, Aloe C, Schiltz AM, Peng RD, Rabinovitch N, Ong MJ, Williams DL, Breyse PN, **Diette GB**, Liu AH. Indoor pollutant exposures modify the effect of airborne

endotoxin on asthma in urban children. *Am J Respir Crit Care Med* 2013 Nov 15;188(10):1210-5.  
PMCID: PMC3863732

126. Okelo SO, Eakin MN, Riekert KA, Teodoro AP, Bilderback AL, Thompson DA, Loiaza-Martinez A, Rand CS, Thyne S, **Diette GB**, Patino CM. Validation of parental reports of asthma trajectory, burden, and risk by using the pediatric asthma control and communication instrument. *J Allergy Clin Immunol Pract* 2014 Mar-Apr; 2(2):186-192.
127. Okelo SO, Riekert KA, Eakin M, Bilderback A, Rand CS, **Diette GB**, Yenokyan G. Pediatrician qualifications and asthma management behaviors and their association with patient race/ethnicity. *J Asthma* 2014 Mar;51(2):155-161.
128. Sharma S, Zhou X, Thibault DM, Himes BE, Liu A, Szeffler SJ, Strunk R, Castro M, Hansel NN, **Diette GB**, Vonakis BM, Adkinson NF Jr, Avila L, Soto-Quiros M, Barraza-Villareal A, Lemanske RF Jr, Solway J, Krishnan J, White SR, Cheadle C, Berger SAE, Fan J, Boorgula MP, Nicolae D, Gilliland F, Barnes K, London SJ, Martinez F, Ober C, Celedon JC, Carey VJ, Weiss ST, Raby BA. A genome-wide survey of CD4 lymphocyte regulatory genetic variants identifies novel asthma genes. *J Allergy Clin Immunol* 2014; 134(5): 1153-1162.
129. Peng RD, Butz A, Hacksta A, Williams DL, **Diette GB**, Breyse P, Matsui E. Estimating the health benefit of reducing indoor air pollution in a randomized environmental intervention. *J Royal Statistical Society.* 2015; 178(2): 425-443.
130. Williams DL, McCormack M, Matsui EC, **Diette GB**, McKenzie SE, Geyh AS, Breyse PN. Cow allergen (Bos d 2) and Endotoxin Concentrations are higher in the settled dust of homes proximate to industrial scale dairy operations. *Journal of Exposure Science & Environmental Epidemiology.* Advance online publication] DOI: JES.2014.57, 2014
132. Hersh CP, Make BJ, Lynch DA, Barr RG, Bowler RP, Calverley PM, Castaldi PJ, Cho MH, Coxson HO, DeMeo DL, Foreman MG, Han MK, Harshfield BJ, Hokanson JE, Lutz S, Ramsdell JW, Regan EA, Rennard SI, Schroeder JD, Sciurba FC, Steiner RM, Tal-Singer R, van Beek E Jr, Silverman EK, Crapo JD, COPDGene and ECLIPSE Investigators. Non-emphysematous chronic obstructive pulmonary disease is associated with diabetes mellitus. *BMC Pulm Med.* 2014; 14: 164.
133. Kim V, Desai P, Newell JD, Make BJ, Washko GR, Silverman EK, Crapo JD, Bhatt SP, Criner GJ, COPDGene Investigators. Airway wall thickness is increased in COPD patients with bronchodilator responsiveness. *Respir Res.* 2014; 15:84.
134. Vachani A, Tanner NT, Aggarwal J, Mathews C, Kearney P, Fang KC, Silvestri G, **Diette GB**. Factors that influence physician decision making for indeterminate pulmonary nodules. *Annals of American Thoracic Society.* 2014; 11(10): 1586-1591.
135. Kaji DA, Belli AJ, McCormack MC, Matsui EC, Williams DL, Paulin L, Putcha N, Peng RD, **Diette GB**, Breyse PN, Hansel NN. Indoor pollutant exposure is associated with heightened respiratory symptoms in atopic compared to non-atopic individuals with COPD. *BMC Pulm Med.* 2014; 14:147.
136. Hackstadt AJ, Matsui EC, Williams DL, **Diette GB**, Breyse PN, Butz AM, Peng RD. Inference for environmental intervention studies using principal stratification. *Stat Med.* 2014; 33(28): 4919-4933.

137. Lee JH, McDonald ML, Cho MH, Wan ES, Castaldi PJ, Hunninghake GM, Marchetti N, Lynch DA, Crapo JD, Lomas DA, Coxson HO, Bakke PS, Silverman EK, Hersh CP; COPDGene and ECLIPSE Investigators. DNAH5 is associated with total lung capacity in chronic obstructive pulmonary disease. *Respir Res.* 2014; 15:97.
138. Wan ES, Castaldi PJ, Cho MH, Hokanson JE, Regan EA, Make BJ, Beaty TH, Han MK, Curtis JL, Curran-Everett D, Lynch DA, DeMeo DL, Crapo JD, Silverman EK; COPDGene Investigators. Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry (PRISm) in COPDGene. *Respir Res.* 2014; 15:89.
139. Brigham EP, Kolahdooz F, Hansel N, Breyse PN, Davis M, Sharma S, Matsui EC, **Diette GB**, McCormack M. Association Between Western Diet Pattern and Adult Asthma: A Focused Review. *Annals of Allergy, Asthma & Immunology.* 2015; 114(4): 273-80.
140. Paulin LM, **Diette GB**, Blanc PD, Putcha N, Eisner MD, Kanner RE, Belli AJ, Christenson S, Tashkin DP, Han M, Barr RG, Hansel NN, SPIROMETRICS Research Group. Occupational Exposures are Associated with Worse Morbidity in Patients with COPD. *Am J Respir Crit Care Med.* 2015; 191(5): 557-565.
141. Jaganath D, Miranda JJ, Gilman RH, Wise RA, **Diette GB**, Miele CH, Bernabe-Ortiz A, Checkley W, CHONICAS Cohort Study Group. Prevalence of chronic obstructive pulmonary disease and variation in risk factors across four geographically diverse resource-limited settings in Peru. *Respiratory Research.* 2015; 16(1):40.
142. Kolahdooz F, Butler JL, Christiansen K, **Diette GB**, Breyse PN, Hansel NN, McCormack MC, Sheehy T, Gittelsohn J, Sharma S. Food and Nutrient Intake in African American Children and Adolescents Aged 5 to 16 Years in Baltimore City. *Journal of the American College of Nutrition.* 2015; 9:1-12.
143. **Diette GB**, Dalal AA, D'Souza Ao, Lunacsek OE, Nagar SP. Treatment patterns of chronic obstructive pulmonary disease in employed adults in the United States. *International Journal of Chronic Obstructive Pulmonary Disease.* 2015; 10:415-22.
144. McCormack MC, Belli AJ, Kahi DA, Matsui EC, Brigham EP, Peng RD, Sellers C, Williams DL, **Diette GB**, Breyse PN, Hansel NN. Obesity as a susceptibility factor to indoor particulate matter health effects in COPD. *Eur Respir J.* 2015; 45(5): 1248-57.
145. Bose S, Hansel NN, Tonorezos ES, Williams DL, Bilderback A, Breyse PN, **Diette GB**, McCormack MC. Indoor particulate matter associated with systemic inflammation in COPD. *Journal of Environmental Protection.* 2015; 6: 566-72.
146. Sussan T, Gajghate S, Chatterjee S, Mandke P, McCormick S, Sudini K, Kumar S, Breyse P, **Diette GB**, Sidhaye V, Biswal S. Nrf2 reduces allergic asthma in mice through enhanced airway epithelial cytoprotective function. *American Journal of Lung Cell Mol Physiol.* 2015; 309(1):L27-36.
147. Lerner AG, Bernabé-Ortiz A, Ticse R, Hernandez A, Huaylinos Y, Pinto ME, Málaga G, Checkley W, Gilman RH, Miranda JJ; CRONICAS Cohort Study Group. Type 2 diabetes and cardiac autonomic neuropathy screening using dynamic pupillometry. *Diabet Med.* 2015 Nov; 32(11): 1470-8.

148. Schwartz NG, Rattner A, Schwartz AR, Mokheles B, Gilman RH, Bernabe-Ortiz A, Miranda JJ, Checkley W; CRONICAS Cohort Study Group. Sleep Disordered Breathing in Four Resource-Limited Settings in Peru: Prevalence, Risk Factors, and Association with Chronic Diseases. *Sleep*. 2015 Sept; 38(9): 1451-9.
149. Tanner NT, Aggarwal J, Gould MK, Kearney P, **Diette G**, Vachani A, Fang KC, Silvestri GA. Management of Pulmonary Nodules by Community Pulmonologists: A Multicenter Observational Study. *Chest*. 2015; 148(6):1405-14.
150. Bazo-Alvarez JC, Quispe R, Peralta F, Poterico JA, Valle GA, Burroughs M, Pillay T, Gilman RH, Checkley W, Malaga G, Smeeth L, Bernabé-Ortiz A, Miranda JJ; PERU MIGRANT Study; CRONICAS Cohort Study Group. Agreement Between Cardiovascular Disease Risk Scores in Resource-Limited Settings: Evidence from 5 Peruvian Sites. *Crit Pathw Cardiol*. 2015; 14(2): 74-80.
151. Francis ER, Kuo CC, Bernabe-Ortiz A, Nessel L, Gilman RH, Checkley W, Miranda JJ, Feldman HI; CRONICAS Cohort Study Group. Burden of chronic kidney disease in resource-limited settings from Peru: a population-based study. *BMC Nephrol*. 2015; 16:114.
152. Benziger CP, Bernabé-Ortiz A, Gilman RH, Checkley W, Smeeth L, Málaga G, Miranda JJ; CRONICAS Cohort Study group. Metabolic Abnormalities Are Common among South American Hispanics Subjects with Normal Weight or Excess Body Weight: The CRONICAS Cohort Study. *PLoS One*. 2015; 10(11): e0138968.
153. Lutz SM, Cho MH, Young K, Hersh CP, Castaldi PJ, McDonald ML, Regan E, Mattheisen M, DeMeo DL, Parker M, Foreman M, Make BJ, Jensen RL, Casaburi R, Lomas DA, Bhatt SP, Bakke P, Gulsvik A, Crapo JD, Beaty TH, Laird NM, Lange C, Hokanson JE, Silverman EK; ECLIPSE Investigators.; COPDGene Investigators. A genome-wide association study identifies risk loci for spirometric measures among smokers of European and African ancestry. *BMC Genet*. 2015; 16:138.
154. Bernabé-Ortiz A, Carrillo-Larco RM, Gilman RH, Checkley W, Smeeth L, Miranda JJ; CRONICAS Cohort Study Group. Contribution of modifiable risk factors for hypertension and type-2 diabetes in Peruvian resource-limited settings. *J Epidemiol Community Health*. 2016; 70(1): 49-55.
155. Quispe R, Bazo-Alvarez JC, Burroughs Peña MS, Poterico JA, Gilman RH, Checkley W, Bernabé-Ortiz A, Huffman MD, Miranda JJ; PERU MIGRANT Study.; CRONICAS Cohort Study Group. Distribution of Short-Term and Lifetime Predicted Risks of Cardiovascular Diseases in Peruvian Adults. *J Am Heart Assoc*. 2015; 4(8): e002112.
156. Miele CH, Jaganath D, Miranda JJ, Bernabe-Ortiz A, Gilman RH, Johnson CM, **Diette GB**, Wise RA, Checkley W; CRONICAS Cohort Study Group. Urbanization and Daily Exposure to Biomass Fuel Smoke Both Contribute to Chronic Bronchitis Risk in a Population with Low Prevalence of Daily Tobacco Smoking. *COPD*. 2016; 13(2): 186-95.
157. Ruiz-Grosso P, Miranda JJ, Gilman RH, Walker BB, Carrasco-Escobar G, Varela-Gaona M, Diez-Canseco F, Huicho L, Checkley W, Bernabe-Ortiz A; CRONICAS Cohort Study Group. Spatial distribution of individuals with symptoms of depression in a periurban area in Lima: an example from Peru. *Ann Epidemiol*. 2016; 26(2): 93-9.

158. Gaviola C, Miele CH, Wise RA, Gilman RH, Jaganath D, Miranda JJ, Bernabe-Ortiz A, Hansel NN, Checkley W; CRONICAS Cohort Study Group. Urbanisation but not biomass fuel smoke exposure is associated with asthma prevalence in four resource-limited settings. *Thorax*. 2016; 71(2): 154-60.
159. Sulaiman I, Mac Hale E, Holmes M, Hughes C, D'Arcy S, Taylor T, Rapcan V, Doyle F, Breathnach A, Seheult J, Murphy D, Hunt E, Lane SJ, Sahadevan A, Crispino G, **Diette G**, Killane I, Reilly RB, Costello RW. A protocol for a randomised clinical trial of the effect of providing feedback on inhaler technique and adherence from an electronic device in patients with poorly controlled severe asthma. *BMJ Open*. 2016; 6(1): e009350.
160. Engelgau MM, Sampson UK, Rabadan-Diehl C, Smith R, Miranda J, Bloomfield GS, Belis D, Narayan KM; National Health, Lung, and Blood Institute–UnitedHealth Global Health Centers of Excellence Collaborators. Tackling NCD in LMIC: Achievements and Lessons Learned From the NHLBI-UnitedHealth Global Health Centers of Excellence Program. *Glob Heart*. 2016; 11(1): 5-15.
161. Zavala-Loayza JA, Benziger CP, Cárdenas MK, Carrillo-Larco RM, Bernabé-Ortiz A, Gilman RH, Checkley W, Miranda JJ; CRONICAS Cohort Study Group. Characteristics Associated With Antihypertensive Treatment and Blood Pressure Control: A Population-Based Follow-Up Study in Peru. *Glob Heart*. 2016; 11(1): 109-19.
162. Quispe R, Benziger CP, Bazo-Alvarez JC, Howe LD, Checkley W, Gilman RH, Smeeth L, Bernabé-Ortiz A, Miranda JJ; CRONICAS Cohort Study Group. The Relationship Between Socioeconomic Status and CV Risk Factors: The CRONICAS Cohort Study of Peruvian Adults. *Glob Heart*. 2016; 11(1): 121-130.e2.
163. Sudini K, **Diette GB**, Breyse PN, McCormack MC, Bull D, Biswal S, Zhai S, Brereton N, Peng RD, Matsui EC. A Randomized Controlled Trial of the Effect of Broccoli Sprouts on Antioxidant Gene Expression and Airway Inflammation in Asthmatics. *J Allergy Clin Immunol Pract*. 2016; 4(5): 932-40.
164. McCormack MC, Belli AJ, Waugh D, Matsui EC, Peng RD, Williams DL, Paulin L, Saha A, Aloe CM, **Diette GB**, Breyse PN, Hansel NN. Respiratory Effects of Indoor Heat and the Interaction with Air Pollution in Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc*. 2016; 13(12): 2125-2131.
165. Peters KO, Williams AL, Abubaker S, Curtin-Brosnan J, McCormack MC, Peng R, Breyse PN, Matsui EC, Hansel NN, **Diette GB**, Strickland PT. Predictors of polycyclic aromatic hydrocarbon exposure and internal dose in inner city Baltimore children. *J Expo Sci Environ Epidemiol*. 2017; 27(3): 290-298.
166. Ludwig S, Jimenez-Bush I, Brigham E, Bose S, **Diette G**, McCormack MC, Matsui EC, Davis MF. Analysis of home dust for *Staphylococcus aureus* and staphylococcal enterotoxin genes using quantitative PCR. *Sci Total Environ*. 2017; 581-582: 750-755.
167. Bernabé-Ortiz A, Carrillo-Larco RM, Gilman RH, Checkley W, Smeeth L, Miranda JJ; CRONICAS Cohort Study Group. Impact of urbanisation and altitude on the incidence of, and risk factors for, hypertension. *Heart*. 2017; In Press.

# **EXTRAMURAL FUNDING:**

## **Current Funding:**

- 09/01/2015-08/31/2019      Obesity Enhances Susceptibility to Pollutant Effects in Asthma  
NIH/NIEHS P50ES018176  
Annual Direct: \$1,051,797  
PI: Hansel  
Role: Co-Director, 25%  
OBesity Enhances Susceptibility to Pollutant Effects in Asthma (OBESE ASTHMA), will study mechanisms by which obesity leads to enhanced susceptibility to pollutants (particulate matter with aerodynamic diameter < 2.5 µm (PM2.5) and ultrafine particles (UFP)) leading to increased asthma morbidity in children.
- 07/01/2015-06/30/2020      Comparing Urban and Rural Effects of Poverty on COPD (CURE COPD)  
NIH/NIEHS P50ES026096  
Annual Direct: \$693,432  
PI: Hansel  
Role: Co-Director, 5%  
Comparing Urban and Rural Effects of Poverty on COPD (CURE COPD)  
Annual Direct Cost: \$693,432 Principal Investigator, 23% effort The aim of our Center, Comparing Urban and Rural Effects of poverty on COPD (CURE COPD), is to understand these interactive effects (high indoor air pollution, obesity and pro-inflammatory diets) in both urban (Project 1) and rural (Project 2) low income communities, both of which suffer disproportionate prevalence and morbidity from COPD.
- 09/01/2012-08/31/2017      K-24 Mentoring and Patient Oriented Research in Asthma  
NIH/NIEHS K24ES021098  
Annual Direct: \$182,540.00  
Grant Number 1133451  
PI: Diette  
Role: Principal Investigator, 6.0 calendar months  
A major focus of this proposal will be to expand the present research program from inner city children to also include inner city adults with asthma. With this expansion in the research program, the candidate will provide the foundation for future trials in adults of home-based multi-component environmental interventions, goals which are concordant with the career goals of current mentees and will establish the infrastructure for future mentees with a research interest in adult asthma
- 09/01/2009-07/31/2015      Title: Mechanisms of asthma-dietary interventions against environmental triggers (No cost extension)  
P01 ES018176  
NIH/NIEHS/EPA  
Total Direct \$4,999,821 (\$970,685 Year 3)  
PI/PD: Diette  
Roles: Program Director, Administrative Core Leader, Project 1 Leader. 3.0 calendar months

Goals: The long-term goal of the **ASTHMA-DIET** (A Study to understand The Mechanisms of Asthma--Dietary Interventions to protect against Environmental Triggers) Program is to understand how diet influences the asthmatic response to indoor and outdoor airborne pollutants and allergens, with the expectation of translating these findings into practical dietary strategies to improve pediatric asthma health.

- 09/07/2010-04/30/2015 Genetic susceptibility to asthma and indoor air pollution in Peru  
R01 ES018845  
NIH/NIEHS  
Annual Direct Cost: \$433,836  
PI: Hansel  
Role: Co-Investigator, 1.20 calendar months  
The goal of this proposal is to examine the contribution of genetic susceptibility to the adverse effects of indoor air pollution (particulate matter and nitrogen dioxide) on asthma health in a Hispanic population.
- 02/18/2011-12/31/2015 Statistical methods for complex environmental health data.  
R01 ES019560  
NIH/NIEHS  
Annual Direct: \$243,746  
PI: Peng  
Role: Co-Investigator, 0.60 calendar months  
This project will develop a spatial-temporal Bayesian hierarchical multivariate receptor model for identifying sources of air pollution chemical mixtures and estimating their effect on population health outcomes. Innovation focuses on (a) conducting an integrated national assessment of the health effects of pollution sources; (b) the use of spatial-temporal models for source apportionment; and (c) the introduction of national databases on source profiles and emissions to inform model development and parameter estimation. These methods will be applied to data from a national study of air pollution and health outcomes, the Medicare Cohort Air Pollution Study, to (a) estimate short-term population health effects of PM sources on a national, regional, and local scale; (b) estimate short- and long-term health effects of PM constituents and identify the sources of toxic constituents

#### **PAST (most recent 5 years only)**

- 09/14/2007-08/31/2013 SCCOR: Mechanisms and Treatment of COPD Progression  
(NCE) 1P50HL084945-01  
NIH/NHLBI  
Annual Direct \$1,957,399  
Program Director: Wise  
Role: Core C Leader, 1.2 calendar months  
The overall goal of this SCCOR program is to understand the complex interplay of mechanisms that promote the progression of COPD and to translate that understanding into treatments that can benefit persons who suffer from COPD.
- 09/29/2007-06/30/2013 Center for Childhood Asthma in the Urban Environment

(NCE)	The Role of Particulate Matter and Allergens in Oxidative Stress in Asthma (DISCOVER) 1P50ES015903 NIH/NIEHS Annual Direct \$ 1,607,733 PI/PD: Breyse Roles: Co-Program Director; Project Leader, Project 1 (1.2 calendar months); Co-Investigator, Administrative Core (1.8 calendar months) The long-term goals of this Center are to examine how exposures to environmental pollutants and allergens may relate to airway inflammation and respiratory morbidity in children with asthma living in the inner city of Baltimore, and to search for new ways to reduce asthma morbidity by reducing exposure to these agents.
07/01/2008-06/30/2013	The Impact of Indoor Particulate Matter Exposure on Non-allergic Asthma 5K23 ES016819 NIH/NIEHS Total Direct: \$755,875 PI: McCormack Role: Mentor, no salary support K23 Mentored Patient-Oriented Research Career Development Award The goal of this project is to examine adverse effects of coarse indoor PM. Using a study design that combines a longitudinal panel study and an exposure challenge model the research will demonstrate a causal relationship between indoor coarse PM exposure and exacerbation of asthma status.
07/01/2010-06/30/2012	Vitamin D and Susceptibility to Inhaled Pollutants in Urban Children with Asthma NIH Total Direct: \$187,645 PI: Bose Role: Primary Mentor NRSA. The goal of this study is to identify the role of vitamin D upon the effects of inhaled pollutants upon asthma severity in inner-city children.
07/01/2011-09/24/2012	Interventions to Modify Adherence to Asthma Guidelines HHSA 290 2007 10061 I Agency: AHRQ Annual Direct Costs: \$260,643 PI: Eric Bass Role: Co-PI The objective of this CER is to determine the comparative effectiveness of interventions to modify the adherence of health care providers to asthma guidelines.
12/15/2008-12/14/2011	Intervention trial to reduce nitrogen dioxide and carbon monoxide concentrations in Baltimore City homes FR-5200-N-01A HUD Annual Direct \$271,415

	<p>PI: Hansel Role: Co-Investigator, 0.96 calendar months The purpose of this research is to conduct a randomized intervention trial aimed at reducing indoor nitrogen dioxide and carbon monoxide concentrations in homes.</p>
<p>07/08/2009-06/30/2011</p>	<p>Effect of Fenzian treatment on symptoms, pulmonary function and Albuterol use in patients with mild persistent asthma: A multi-center, sham-controlled clinical trial Fenzian, Inc. (Formerly Eumedics) Annual Direct: \$88,433 PI: Diette, 1.20 calendar months The purpose of the study is to test the efficacy of Fenzian treatment over five weeks to improve asthma control, pulmonary function, symptoms and bronchodilator use.</p>
<p>07/01/2006-06/30/2011</p>	<p>Mouse Allergen and Inner-City Asthma 1R01 A1070630-01 NIH/NIAAD Annual Direct \$225,000 PI: Matsui Role: Co-Investigator, 0.60 calendar months The primary aims of this project are (1) to examine the link between household mouse allergen exposure and asthma morbidity, and (2) to determine the diagnostic utility of allergy skin testing in predicting allergic airways responses to mouse allergen.</p>
<p>12/26/2003-01/30/2011</p>	<p>Evaluation of home automated tele-management in COPD. R01 AI070630 NIH Annual Direct: \$225,000 PI: Finkelstein Role: Co-Investigator, 0.60 calendar months The goal of this project is to evaluate the impact of home tele-management in COPD patients.</p>
<p>12/01/2005-11/30/2010</p>	<p>A Multicenter Randomized Clinical Trial: Asthma Intervention Research (AIR2 Trial) Asthmatix, Inc Annual Direct \$313,504 PI: Yung Role: Co-Investigator, 0.12 calendar months The goal of this trial is to assess the safety and effectiveness of the Alair system for the treatment of asthma.</p>
<p>11/1/2003-10/31/2009</p>	<p>Center for Childhood Asthma in the Urban Environment P01 R-826724/P01 ES09606 (Breyse) NIH/EHS/EPA Annual Direct \$918,780 PI: Breyse</p>

Roles: Deputy Program Director; PI of Epidemiology Component, Co-Investigator, 1.5 calendar months

The long term goals of this Center were to examine how exposures to environmental pollutants and allergens might relate to airway inflammation and respiratory morbidity in children with asthma living in the inner city of Baltimore, and to search for new ways to reduce asthma morbidity by reducing exposure to these agents.

09/30/2003-06/30/2009

SCCOR: Ventilator associated lung injury: Molecular approaches

P50 HL073944-03 (Brower)

NIH/NHLBI

Annual Direct \$2,790,934

PI/PD: Brower

Role: Core Leader, Core B, Data Management Core, 0.60 calendar months

This SCCOR was focused on understanding the complex interplay between mechanical ventilation and the increased morbidity and mortality associated with acute lung injury. The application had interactive Cores using state of the art approaches to provide understanding of critical pathobiologic processes in ventilator-associated lung injury and to define key genetic determinants relevant to acute lung injury.

09/30/2004-08/31/2009

Genetics of Asthma Severity and Lung Function Decline

K23 HL76322 -02

NIH/NHLBI

Annual Direct \$148,250

PI: Hansel

Role: Primary Mentor, effort as needed

The goal of this study was to identify genetic polymorphisms that mark high risk individuals for early intervention to decrease asthma morbidity.

09/10/2001-08/31/2006

Improving physician adherence to asthma guidelines

K23 HL04266

NIH

Annual Direct \$146,772

Role: Principal Investigator, 9.0 calendar months

Provide mentored training and research period for early career development.

Improve physician adherence to national asthma guidelines

09/01/2002-07/31/2007

Baltimore Asthma Severity Study

R01 HL67905 (Ford)

NIH

Annual Direct \$443,417

PI: Ford

Role: Co-Investigator, 0.6 calendar months

The objective of this study was to provide insight into the genes controlling susceptibility to human asthma and promote the development of novel therapeutics.

9/01/2002-08/31/2007

Improving Respiratory Outcomes in ALS

	<p>K23 HL67887 (Lechtzin) NIH Annual Direct \$121,750 PI: Lechtzin Role: Advisor (effort as needed) The overall theme of this award is to study various aspects of non-invasive positive pressure ventilation in patients with ALS with the goal of improving respiratory management of these patients.</p>
<p>2007-2008 (NCE)</p>	<p>Howard/Hopkins Center for Reducing Asthma Disparities HL072455 NIH/NHLBI Annual Direct \$513,475 PI: Rand Role: Leader, Project 1, 1.5 calendar months, no cost extension This application presents four research projects designed to collaboratively investigate factors associated with the disproportionate burden of asthma experienced by inner-city, African-American children and adults.</p>
<p>09/30/2004-06/30/2008</p>	<p>Improving asthma care for minority children in Head Start R18 HL73833 NIH Annual Direct \$625,506 PI: Rand Role: Co-Investigator, 0.6 calendar months The goal of this project is to study the effect communication intervention on asthma-related morbidity and mortality among low-income African American children.</p>
<p>02/23/2004-12/31/2006</p>	<p>A randomized, sham-controlled, double-blinded pilot study to assess the effect of high frequency chest wall oscillation therapy in patients with chronic bronchitis Advanced Respiratory PI: Diette, 0.12 calendar months</p>
<p>10/01/2007-09/30/2009</p>	<p>Randomized clinical trial Protocol #: CQAB149B2335S Novartis Total Direct Costs: \$161,368 PI: Diette, 1.20 calendar months A 26-week treatment, multicenter, randomized, double-blind, double dummy, placebo-controlled, adaptive, seamless, parallel-group study to assess the efficacy, safety and tolerability of two doses of indacaterol (selected from 75, 150, 300 &amp; 600 ug o.d.) in patients with chronic obstructive pulmonary disease using blinded formoterol (12 ug b.i.d.) and open label tiotropium (18 ug o.d.) as active controls.</p>

## EDUCATIONAL ACTIVITIES

### Educational Publications

#### Invited Review Articles

1. Robinson L, Diette GB. Best Practices for Insertion of Central Venous Catheters in Intensive Care Units to Prevent Catheter-Related Bloodstream Infections. *Journal of Laboratory and Clinical Medicine* 2004;143:5-13.
2. Sharma HP, Hansel NN, Matsui EC, Diette GB, Eggleston PA, Breysee PN. Indoor Environmental Influences on Children's Asthma. *Pediatric Clinics North America*. 2007;54:103-120
3. Hansel NN and Diette GB. Gene Expression Profiling in Human Asthma. *Proc Am Thorac Soc*. 2007; 4(1):32-6.
4. **Diette GB**, Rand C. The Contributing Role of Health-Care Communication to Health Disparities for Minority Patients with Asthma. *Chest*. 2007 Nov;132(5 Suppl):802S-9S.
5. **Diette GB**, McCormack MC, Hansel NN, Breysee PN, Matsui EC. Environmental issues in managing asthma. *Respiratory Care*. 2008;53(5):602-15; discussion 616-7.
6. Matsui EC, Hansel NN, McCormack MC, Rusher R, Breysee P, **Diette GB**. Asthma in the Inner City and the Indoor Environment. *Immunology Allergy Clinics North America*. 2008;28:665-686.
7. Okelo SO, Butz AM, Sharma R, **Diette GB**, Pitts SI, King TM, Linn ST, Reuben M. Chelladurai Y, Robinson KA. Interventions to modify health care provider adherence to asthma guidelines: A systemic review. *Pediatrics*. 2013 Sep;132(3):517-34.

#### Editorials

1. Krishnan JA, **Diette GB**, Rand CS. Disparities in Outcomes from Chronic Disease: Impaired Patient-Physician Partnerships May Be an Important Cause in Minorities. *British Medical Journal* 2001;323:950.
2. Alberg A, **Diette GB**, Ford J. Attendance and absence as markers of health status: The example of active and passive cigarette smoking. *American Journal of Epidemiology* 2003 May 15;157(10):870-3.
3. **Diette GB**, Clinical Commentary: Overuse of  $\beta$ 2-agonists. *J Resp Diseases* 2000;21:721.

#### Case Reports

None.

#### Letters

1. Patil S, Krishnan JA, Lechtzin N, **Diette GB**. In-hospital mortality following acute exacerbation of chronic obstructive pulmonary disease. *Archives of Internal Medicine*. 2004 Jan 26;164:222-223.
2. **Diette GB**, Wu AW. Elderly asthmatic patients. *Archives of Internal Medicine*. 2003 Jan 13;163:1:122.

4. Clerisme-Beaty EM, Rand C, **Diette GB**. Reply to Farah. Weight loss in asthma: More evidence is needed. Reply to Farah. *Journal of Allergy and Clinical Immunology* 2010 125(3):770. PMID: PMC2908807.

#### Book Chapters:

1. **Diette G**, Brower R. Traditional Invasive Ventilation. In, Pulmonary Respiratory Therapy Secrets, 2<sup>nd</sup> Edition, Parsons P and Heffner J, Eds., Philadelphia, Hanley & Belfus, 2002.
2. **Diette G**, Brower R. Traditional Invasive Ventilation. In, Pulmonary Respiratory Therapy Secrets, Parsons P and Heffner J, Eds., Philadelphia, Hanley & Belfus, 1997.
3. **Diette G**. Pleural Effusion. In, *Mosby's Success in Medicine Specialty Clinical Sciences*, Donnelly JL, Ed., Mosby, 1996.
5. **Diette G**. Pneumothorax. In, *Mosby's Success in Medicine Specialty Clinical Sciences*, Donnelly JL, Ed., Mosby, 1996.
6. **Bose S, Diette GB**. Health disparities related to environmental air quality. In: *Health Disparities in Respiratory Medicine*. Eds: Gerald L and Berry C. Springer. In press.

#### Internet:

**Diette GB**, Liu MC. Disease Update on Asthma. Medcast Networks. [Released March 1, 1999]

Okelo SO, Butz AM, Sharma R, **Diette GB**, Pitts SI, King TM, Linn ST, Reuben M, Chelladurai Y, Robinson KA. Interventions to modify health care provider adherence to asthma guidelines [Internet]. Rockville MD: Agency for Healthcare Research and Quality (US); 2013 May.

#### Reports:

1. Wu A, **Diette GB**, Skinner E, Clark R, Steinwachs D. Treatment Patterns Among Adult Asthmatics: Factors Associated with High Use of Inhaled  $\beta$ -agonists, Low Use of Inhaled Corticosteroids, and Nocturnal Symptoms. Submitted to Merck & Co., Inc., July 1997.
2. Steinberg EP, Holtz PM, Greenwald TP, **Diette GB**, Wills S, Webb A, Daugherty L, Caravoulas CL, Gabrielsen M, Pomponio C. Report of results of a pilot test of draft NCQA HEDIS measures of health plan performance in control of blood pressure among diagnosed hypertensives. Submitted to the NCQA Hypertension Measure Advisory Committee, July 1998.
3. Wu AW, Skinner EA, **Diette GB**, Nguyen TTH, Clark RD. Quality of Care and Outcomes for Childhood Asthma in Managed Care: Validation of the Asthma Therapy Assessment Questionnaire. Submitted to Merck & Co., Inc., November 1998.
4. **Diette GB**, Krishnan JA, Lechtzin N, Belcastro D. Evidence Report on Chronic Obstructive Pulmonary Disease: Treatment and Risks. Submitted to CardioContinuum, September 1999.
5. Wu AW, **Diette GB**, Dominici F, Skinner EA. The 1998 Asthma Outcomes Survey: Phase I Final Report. Submitted to the Pacific Business Group on Health, October 1999.

6. **Diette GB**, Krishnan JA, Lechtzin N, Belcastro D. Report on Focus Group of Clinician Experts on Treatment of Chronic Obstructive Pulmonary Disease. Submitted to CardioContinuum, September 1999.
7. **Diette GB**, Qutami M, Sullivan B. Report on Cystic Fibrosis Utilization and Asthma Utilization and Medication Use. Submitted to Aerogen, December 1999.
8. **Diette GB**, Rand C, Wise RA, Thompson K, Merriman B. Pilot Study of Alternative Treatment Settings of High Frequency Chest Wall Oscillation in Patients with Chronic Bronchitis. Submitted to Advanced Respiratory, Inc, December 2003.

## Teaching

### Classroom Instruction

- |             |  |
|-------------|--|
| 1993-1994   | Instructor, Course on Clinical Management in the Emergency Department, University of Pennsylvania Department of Emergency Medicine                                     |
| 12/1993     | Instructor, First Aid for First Year Medical Students, University of Pennsylvania School of Medicine   |
| 1996 & 1999 | Clinical Faculty for Human Anatomy Discussion Group, Heart and Lungs, Johns Hopkins University School of Medicine  |
| 1997-2000   | Instructor, Evidence-Based Medicine Rotation for Medical Interns, Chronic Obstructive Pulmonary Diseases, Department of Medicine, Johns Hopkins Bayview Medical Center |
| 1997 & 2000 | Discussion Leader, Organ Systems Course, Pulmonary Physiology Section, Johns Hopkins University School of Medicine   |
| 1997        | Teaching Assistant, The Science of Clinical Investigation: Design of Clinical Studies. Johns Hopkins University School of Hygiene and Public Health                    |
| 1998        | Lecturer, Clinical Skills Course: The Pulmonary Examination, Johns Hopkins University School of Medicine   |
| 1999 & 2000 | Discussion Leader, Pathophysiology Course, Pathophysiology of Shock, Johns Hopkins University School of Medicine   |
| 1999        | Lecturer, Advanced Research Methods, International Respiratory Epidemiology Course, American Thoracic Society, Cusco, Peru   |
| 1999-2002   | Co-Director. The Science of Clinical Investigation: Design of Clinical Studies. Johns Hopkins University School of Hygiene and Public Health                           |
| 2000-2003   | Lecturer, Patient Outcomes and Quality of Care Course, Department of Health Policy and Management, Johns Hopkins University School of Hygiene and Public Health        |
| 2000        | Lecturer, Advance Research Methods, International Respiratory Epidemiology Course,   |

American Thoracic Society, Quinamavida, Chile

- 2001 Discussion Leader, Clinical Epidemiology, Department of Epidemiology, Johns Hopkins University, April 2001.
- 2003 Co-Director. Advanced Research Methods, International Respiratory Epidemiology Course, American Thoracic Society, Buenos Aires, Argentine
- 2004 Director. Advanced Research Methods, Method in Epidemiologic, Clinical and Operations Research, American Thoracic Society, Punta del Este, Uruguay
- 2005 Faculty. Methods in Clinical Research. ERS/ATS School Course. Prague, Czech Republic,
- 2005 Director. Advanced Research Methods, Methods in Epidemiologic, Clinical and Operations Research, American Thoracic Society, Quito, Ecuador
- 2006 Director. Advanced Research Methods, Methods in Epidemiologic, Clinical and Operations Research, American Thoracic Society, Alphaville, Brazil.
- 2007-Present Attending Physician, the Barker Firm, Johns Hopkins University School of Medicine

### **Continuing Medical Education**

- 2010 Managed care strategies used in the successful treatment of asthma. National Asthma Education and Prevention Program. Medical Communications Media, Inc.

### **Mentoring (pre- and post-doctoral):**

#### **Advisees**

- 2012-Present Emily Bingham, MD  
Post-doctoral Fellow, Division of Pulmonary and Critical Care Medicine
- 2011-Present Laura M. Paulin, MD  
Post-doctoral Fellow, Division of Pulmonary and Critical Care Medicine
- 2012-Present Jessica Rice, MD  
Post-doctoral Fellow, Department of Pediatrics
- 2010-2014 Niru Putcha, MD  
Post-doctoral Fellow, Division of Pulmonary and Critical Care Medicine
- 2010-2011 Daniel Jamieson, MD  
Post-doctoral Fellow, Division of Pulmonary and Critical Care Medicine
- 2009-Present Sonali Bose, MD, MPH  
Post-doctoral Fellow, Division of Pulmonary and Critical Care Medicine  
Research Theme: Vitamin D levels in urban black children with asthma

Current Position: Instructor of Medicine, Pulmonary and Critical Care Medicine

- 2009-2010 Marisha Cook, MD  
Post-doctoral Fellow, Division of Allergy and Clinical Immunology  
Research Theme: Dietary pattern differences by race in asthma  
Current Position: Post-doctoral Fellow, Allergy & Clinical Immunology
- 2008-2009 Timothy Scialla, MD  
Post-doctoral Fellow, Division of Pulmonary and Critical Care Medicine  
Research Theme: Inner City Diet and Asthma  
Current Position: Assistant Professor of Medicine, University of Miami, Miami, Florida
- 2006-2007 Sabine Karem, MD  
Post-doctoral Fellow, Division of Pulmonary and Critical Care Medicine  
Research Theme: Asthma Control in African-Americans  
Current Position: Internal Medicine Resident, Montifiore Hospital, Bronx, NY
- 2005-2006 Lindsey Kim  
MPH student, School of Hygiene and Public Health  
Thesis: Outcomes Study on Environmental Control Practices on Health of Inner-City Children with Asthma
- 2005-2007 Emily Smith Tonorezos  
Post-Doctoral Fellow, Division of General Internal Medicine  
Research Theme: Diabetes as a modifying factor on the effect of particulate matter in COPD  
Current Position: Assistant Professor of Medicine, Memorial Sloan Kettering, New York.
- 2005-2008 Meredith C. McCormack, MD, MHS  
Post-Doctoral Fellow, Division of Pulmonary and Critical Care Medicine  
Awarded Chest Foundation Award for Women's Studies, Loan Repayment Program, NIH K-23 Award, Johns Hopkins Bloomberg School of Public Health Faculty Grant in Global Health, and Pearl M. Stetler Research Fund  
Research Theme: Particulate Matter Effects on Asthma and COPD  
Current Position: Assistant Professor of Medicine, Johns Hopkins University, Baltimore, Maryland
- 2004-2006 Amit Rahman  
Medical Student, Johns Hopkins University, School of Medicine  
Research Theme: Co-Morbidity COPD Outcomes
- 2004-2005 Alan Salas  
Under-represented Minority Summer Research Program  
Undergraduate Student, Johns Hopkins University, Baltimore, MD  
Research Theme: Early Life Exposures and Risk of Asthma
- 2002-2003 Deanna Perez Williams  
Community Health Scholars Program, Kellogg Foundation

- Research Theme: Development of a Culturally-Sensitive, Patient-Focused Asthma Communication Instrument Designed to Enhance Provider-Patient Communication in Hispanics in Baltimore  
Current Position: Howard University
- 2002-2004 Elizabeth C. Matsui, MD  
Post-Doctoral Fellow, Division of Allergy and Immunology, Department of Pediatrics, Johns Hopkins University  
Research Theme: Mouse allergen exposure, antibody responses, prick skin test response and allergy symptoms in laboratory workers  
Current Position: Associate Professor of Pediatrics. Division of Allergy and Immunology, Department of Pediatrics, Johns Hopkins University
- 2002-2004 Necole Streeper, MD  
Minority Summer Research Program  
Research Theme: Physician Underestimation of Self-Management Ability of African-Americans with Asthma  
Current Position: Resident, Dept of Urology, University of Texas HSC, San Antonio, TX
- 2002-2004 James Lee, MD  
Housestaff, Internal Medicine, Johns Hopkins Hospital  
Research Theme: Gender Differences in Childhood Asthma  
Current Position: Assistant Professor of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine, Hospital of the University of Pennsylvania, Philadelphia, PA
- 2002-2007 Cecilia Patino, MD  
Research Associate, Division of Pulmonary and Critical Care Medicine  
Research Theme: (1) Physician Adherence to Asthma Guidelines; (2) Validation of Survey Methods of Environmental Assessment  
Current Position: Assistant Professor, Department of Preventive Medicine, University of Southern California, Los Angeles, CA
- 2001-2003 Marianelle Platon, MD  
Under-represented Minority Summer Research Program  
Research Theme: Validation of Physician Reported Adverse Events during Bronchoscopy  
Current Position: Physician, National Naval Medical Center, Bethesda, Maryland
- 2001-2004 Lucian Davis, MD  
Housestaff, Internal Medicine, Johns Hopkins Hospital  
Research Theme: Predictors of New-Onset Dyspnea in COPD  
Current Position: Assistant Adjunct Professor, Division of Pulmonary and Critical Care Medicine, University of California, San Francisco, San Francisco.
- 2001-2005 Susan Gerhardt, MD  
Post-Doctoral Fellow, Division of Pulmonary and Critical Care Medicine  
Awarded Pearl M. Stetler Research Grant  
Research Theme: Treatment of Bronchiolitis Obliterans in Lung Transplant Rejection  
Current Position: Private Practice, Pennsylvania
- 2000-2005 Lewis J. Robinson, MD

- Post-Doctoral fellow, Division of Pulmonary and Critical Care Medicine  
Research theme: National Guidelines and Central Venous Catheter Infections in the Intensive Care Unit  
Current Position: Assistant Professor, Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle.
- 2000-2003 Sande Okelo, MD  
Post-Doctoral fellow, Division of Pediatric Pulmonary Medicine  
Research theme: Emotional Function and Asthma Morbidity in Children  
Awarded NIEHS Minority Supplement Award  
Awarded ATS Minority Travel Award  
Current Position: Assistant Professor, Department of Pediatrics, David Geffen School of Medicine at UCLA, Mattel Children's Hospital UCLA, Los Angeles, CA
- 2000-2004 Nadia N. Hansel, MD, MHS  
Post-Doctoral fellow, Division of Pulmonary and Critical Care Medicine  
Awarded Howard C. and Jane R. Goodman Award  
Awarded the Baurernschmidt Fellowship Award from Eudowood Foundation  
Awarded Chest Foundation Award for Women's Studies  
Awarded American Thoracic Society Underrepresented Minority Travel Award  
Research themes: 1) Quality of Life in Tuberculosis; 2) Th1/Th2 phenotype in tuberculosis and asthma.  
Current Position: Associate Professor of Medicine, Johns Hopkins University
- 1999-2001 Edward Cox, Jr., MD, MPH  
MPH student, School of Hygiene and Public Health  
Project: Association of Hospital Volume and In-Hospital Mortality among Patients with Community-Acquired Pneumonia  
Current Position: Director, Office of Antimicrobial Products (OAP) Food and Drug Administration, Rockville, Maryland
- 1999-2001 Noah Lechtzin, MD, MPH  
Post-Doctoral fellow, Division of Pulmonary and Critical Care Medicine  
Awarded Travel Award for Poster Presentation at 2001 American Thoracic Society International Meeting  
Research theme: Respiratory manifestations of ALS: 1. Measures of disease burden; 2. Improving patient outcomes.  
Current Position: Associate Professor of Medicine, Johns Hopkins University.
- 1998-2001 Jerry A. Krishnan, MD, PhD  
Post-Doctoral fellow, Division of Pulmonary and Critical Care Medicine.  
Awarded Chest Foundation Research Award for "Assessment of Gender and Race Differences in Quality of Care and Clinical Outcomes from Asthma."  
Research theme: Quality of care and outcomes for asthma by gender and race  
Current Position: Professor of Medicine, University of Illinois, Chicago.
- 1998-1999 Su Wang  
MPH student, School of Hygiene and Public Health

Thesis: Nocturnal Symptoms in Pediatric Asthma: Clinical Features and Health Care Utilization in a Managed Care Setting  
Current Position: Unknown.

1997-2002 Lindy Wolfenden, MD  
Housestaff, Internal Medicine, Johns Hopkins Hospital  
Post-Doctoral Fellow, Division of Pulmonary and Critical Care Medicine  
Research Theme: Older Adults and Asthma  
(Deceased.)

### Thesis committees

07/2014 Kamau Peters, Doctoral Candidate in Environmental Health Sciences.  
Role: Thesis Advisor and Final Oral Examination Committee Member.

04/2013 María Fernanda Cely-García, Doctoral Candidate, Universidad de Los Andes,  
Bogotá Columbia (*Personal exposures to asbestos and respiratory health of automotive mechanics in Bogotá, Columbia*)  
Role: Thesis advisor and Final Oral Defense Committee Member

04/2010 Deanna M. Green, Doctoral Candidate in Environmental Health Sciences  
Role: Thesis Advisor and Final Oral Defense Committee Member

10/2008 Maura Dwyer, Doctoral Candidate in Environmental Health Sciences  
Role: Final Oral Defense Committee Member

10/2007 Juan Ramos Bonilla, Doctoral Candidate in Environmental Health Sciences  
Role: Final Oral Defense Committee Member

12/2006 Sorina Eftin, Doctoral Candidate in Environmental Health Sciences  
Role: Thesis Committee Chair

04/2005 Laura LaRosa, Doctoral Candidate in Environmental Health Engineering  
Role: Final Oral Defense Committee Member

11/2005 Kannika Taenkhum, Doctoral Candidate in Environmental Health Engineering  
Role: Preliminary Orals Committee Member

12/2005 Sande Okele, Doctoral Candidate in Graduate Training Program in Clinical Investigation  
Role: Final Oral Defense Committee Member

09/2004 Lewis Robinson, Doctoral Candidate in Epidemiology  
Role: Final Oral Defense Committee Member

03/2003 Ichan Huang, Doctoral Candidate in Health Policy and Management  
Role: Thesis Committee Chair

03/2002 Ichan Huang, Doctoral Candidate in Health Policy and Management  
Role: Preliminary Orals Committee Member

10/2001 Erika Tang, Doctoral Candidate in Epidemiology  
Role: Preliminary Orals Committee Member

### Editorial Activities

#### Peer review activities

#### Editorial Boards

2010- Present Member, *Clinical Respiratory Journal*  
2013-Present Member, *Journal of Pollution Effects & Control*

**Peer Reviewer**

*American Journal of Respiratory and Critical Care Medicine*  
*Archives of Internal Medicine*  
*Archives of Pediatric and Adolescent Medicine*  
*Cancer Epidemiology, Biomarkers & Prevention*  
*Chest*  
*Epidemiology*  
*Expert Opinion on Pharmacotherapy*  
*Health Services Research*  
*Journal of Allergy and Clinical Immunology*  
*Journal of Clinical Outcomes Management*  
*Journal of General Internal Medicine*  
*Journal of Respiratory Diseases*  
*Medical Care*  
*Pediatrics*  
*Preventative Medicine in Managed Care*  
*Quality of Life Research*  
*Thorax*

**CLINICAL ACTIVITIES:**

**Certification:**

**MEDICAL LICENSURE** Maryland D-47616

**BOARD CERTIFICATION**

1991	National Board of Medical Examiners
1993	American Board of Internal Medicine
1996, 2006	American Board of Internal Medicine, Pulmonary Medicine

**Service Responsibilities (specialty, role, time commitment):**

Intensive Care Medicine, Attending Physician,  
Oncology Center, Pulmonary and Critical Care Service, Attending Physician  
Pulmonary Inpatient Medicine, Attending Physician  
Barker Inpatient Internal Medicine, Attending Physician  
Outpatient Pulmonary Clinic, Attending Physician

**SYSTEM INNOVATION AND QUALITY IMPROVEMENT ACTIVITIES**

**System Innovation and Quality Improvement Publications**

Please see original research citation numbers 2, 3, 4, 6, 7, 9, 11, 12, 13, 14, 15, 17, 20, 21, 22, 23, 24, 26, 27, 29, 30, 31, 34, 36, 42, 43, 44, 45, 47, 52, 59, 68, 69, 70, 73, 75, 76, 81, 84, 88, 89, 92, 93, 95 and 99.

**System Innovation and Quality Improvement efforts within JHM:**

1996-2006	<b>Initiator and Director</b> , Bronchoscopy Quality Improvement Project (BRONCHQI), Johns Hopkins Medical Institutions, Baltimore, MD
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This highly successful project had many findings, including:

1. Documentation of unsafe dosing of lidocaine, which led to a reduction in the strength used from 2% to 1%. Documented no loss of analgesia with the change.
2. Identified risk of bleeding complications with lung biopsy
3. Documented diagnostic utility of having on-site cytopathology services during needle biopsy cases
4. Identified factors associated with patient satisfaction
5. Identified excessive pain and reasons for pain during the procedure
6. Performed a clinical trial of distraction therapy to reduce pain during the procedure
7. Identified predictors of positive diagnostic findings in immune-compromised patients
8. Demonstrated benefits of use of atropine pre-procedure to prevent adverse events

1997-2000      **Member**, Committee for Procedure Review, Pulmonary and Critical Care Medicine Procedures, Johns Hopkins Bayview Medical Center, Baltimore, MD

### **System Innovation and Quality Improvement efforts outside JHM:**

1996-1999      Senior Physician Scientist, Quality Assessment and Improvement Systems Division, Covance Health Economics and Outcomes Services. Washington, D.C.

Dialysis Outcomes Quality Initiative (DOQI): Co-investigator, Medical consultant,  
NCQA HEDIS hypertension measure: Co-investigator on measure validation

2003      **Member**, Howard County Comprehensive Health Improvement Plan for the Year 2010, Howard County Health Department, Columbia, MD

### **National Committee for Quality Assurance**

2003      Member, COPD Technical Subgroup

2004-Present      Member, Clinical Expert Panel

2008      Member, National Committee for Quality Assurance (NCQA) Advisory Panel. HEDIS Trends Publication Expert Advisory Panel.

### **Production of guidelines and/or protocols:**

2002      American Healthways/Johns Hopkins  
2nd Annual Disease Management Outcomes Summit: Standard Outcome Metrics and Evaluation Methodology for Disease Management Programs, November 7-10, 2002, Palm Desert, CA.  
Role: Physician Steering Committee. The outcome metrics remain intact to date.

### **System Innovation and Quality Improvement Program Building/Leadership:**

N/A

### **System Innovation and Quality Improvement Extramural Funding**

12/26/2003-01/30/2011      Evaluation of home automated tele-management in COPD.  
R01 AI070630  
NIH  
Annual Direct: \$225,000  
PI: Finkelstein

09/10/2001-08/31/2006	<p>Role: Co-Investigator, 0.60 calendar months Improving physician adherence to asthma guidelines K23 HL04266 NIH Annual Direct \$146,772</p>
9/01/2002-08/31/2007	<p>Role: Principal Investigator, 9.0 calendar months Provide mentored training and research period for early career development. Improve physician adherence to national asthma guidelines Improving Respiratory Outcomes in ALS K23 HL67887 (Lechtzin) NIH Annual Direct \$121,750 PI: Lechtzin Role: Advisor (effort as needed) The overall theme of this award is to study various aspects of non-invasive positive pressure ventilation in patients with ALS with the goal of improving respiratory management of these patients.</p>
2007-2008 (NCE)	<p>Howard/Hopkins Center for Reducing Asthma Disparities HL072455 NIH/NHLBI Annual Direct \$513,475 PI: Rand Role: Leader, Project 1, 1.5 calendar months, no cost extension This application presents four research projects designed to collaboratively investigate factors associated with the disproportionate burden of asthma experienced by inner-city, African-American children and adults.</p>
09/30/2004-06/30/2008	<p>Improving asthma care for minority children in Head Start R18 HL73833 NIH Annual Direct \$625,506 PI: Rand Role: Co-Investigator, 0.6 calendar months The goal of this project is to study the effect communication intervention on asthma-related morbidity and mortality among low-income African American children.</p>

## ORGANIZATIONAL ACTIVITIES

### Institutional Administrative Appointments

1995-1997	<b>Initiator and Coordinator</b> , Pulmonary and Critical Care Epidemiology Seminar, Johns Hopkins University, Baltimore, MD
1996-present	<b>Initiator and Director</b> , Bronchoscopy Quality Improvement Project (BRONCHQI), Johns Hopkins Medical Institutions, Baltimore, MD
1997-2000	<b>Member</b> , Committee for Procedure Review, Pulmonary and

Critical Care Medicine Procedures, Johns Hopkins Bayview  
Medical Center, Baltimore, MD

- 1999-present **Member**, Education Committee, Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
- 1999-present **Member**, Research Committee, Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
- 1999-2006 **Chair**, Conference Committee, Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
- 1999-present **Member**, Internship Selection Committee, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
- 1999-present **Member**, Fellowship Selection Committee, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
- 2001-present **Member**, Fellow Review Committee, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
- 2003 **Member**, Howard County Comprehensive Health Improvement Plan for the Year 2010, Howard County Health Department, Columbia, MD
- 2003-present **Member**, Faculty Development Committee, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
- 2005 **Member**, Curriculum Reform Committee Meeting, Johns Hopkins School of Medicine, Baltimore, MD
- 2009-present **Member**, Planning Committee, CME Activity – Medical Grand Rounds, Johns Hopkins School of Medicine, Baltimore, MD
- 2011-present **Director**, Obstructive Lung Disease Program, Division of Pulmonary and Critical Care Medicine
- 2013 **Member**, Panel Presentation/Discussion: “writing a successful career development application. Johns Hopkins Professional Development Office, September 25. 2013.
- 2014 *Ad hoc* Committee for a Department of Biostatistics faculty member’s promotion to Associate Scientist.

## Professional Societies

Associate, American College of Physicians (ACP)  
Fellow, American College of Chest Physicians (ACCP)  
Member, American Thoracic Society (ATS)

Member, American Federation for Clinical Research (AFCR)  
Member, Central Society for Clinical Research (CSCR)  
Member, International Society of Environmental Epidemiology

### **Committee Memberships**

#### **American Academy of Allergy, Asthma and Immunology**

2003-Present Member, Genetics and Epidemiology

#### **American Thoracic Society**

1999-2006 Course Faculty Member, Education: Methods in epidemiologic, clinical and operations research (MECOR).  
2002-Present Member, Behavioral Science Assembly Long Range Planning Committee  
2003-Present Member, Behavioral Science Assembly Program Committee  
2003-2004 Chair Elect, Behavioral Science Assembly Program Committee  
2003 Member, IRE/MECOR Planning Retreat Committee  
2004-2005 Chair, Behavioral Science Assembly Program Committee  
2006-2008 Chair, Behavioral Science Assembly  
2006-2008 Member, ATS Board of Directors  
2008-2009 Chair, Behavioral Science Assembly Nominating Committee  
2008-2010 Member, Environmental and Occupational Health Assembly, Clinical Research Committee  
2008-2010 Member, Environmental and Occupational Health Assembly Program Committee  
2008-2010 Member, Environmental and Occupational Health Assembly Working Group on Epidemiology  
2008-2009 Mentor Member, Members in Transition and Training Committee  
2009-2011 Member, Grant Review Committee for ATS Foundation-Tobacco-dependence research fund grant.  
2010-2015 Member, Drug/Device Discovery and Development Committee  
2013-2014 Member, Behavioral Science Assembly Planning Committee  
2013-2014 Member, Behavioral Sciences and Health Services Research Assembly Nominating Committee

#### **National Committee for Quality Assurance**

2003 Member, COPD Technical Subgroup  
2004-Present Member, Clinical Expert Panel

#### **Pennsylvania Department of Health**

2004 Member, Grant Review Committee, Centers of Excellence for Research on Lung Disease Review Panel. Washington, DC.  
2010-2011 Member, Pennsylvania Final Performance Review, Master Tobacco Settlement for the Pennsylvania Department of Health, 09-10 Cycle B

#### **State of Maryland**

2006-2007 Member, Governor-elect Martin O'Malley's Transition Committee, State of Maryland, Department of Health and Mental Hygiene, December, 2006 to January, 2007.

#### **Clinical Trials & Surveys Corp (C-TASC)**

2009-present Member, Institutional Review Board

**Qatar National Research Fund**

2010-present Reviewer, National Priorities Research Program

**Netherlands Asthma Foundation**

2012-present Member, Grant Review Section

**Conference Organizer, Session Chair** (see also Classroom Instruction, pages 19-20)

2003 Chair, American Thoracic Society International Conference Session: Assessing Patient Health, Healthcare and Outcomes: Limits of Physician Estimation

Facilitator, American Thoracic Society International Conference Session: Environmental and Genetic Risk Factors for Pediatric Lung Disease.

Chair, American Thoracic Society International Conference Symposium: Impact of Psychosocial Factors on Respiratory Health.

2004 Chair, American Thoracic Society International Conference Symposium: Assessing Asthma Severity and Asthma Control According to National Guidelines: Are our Assessments Working?

Chair, American Thoracic Society International Conference Symposium: Diagnosis and Outcomes in Pediatric Asthma.

Chair, American Thoracic Society International Conference Symposium: Pediatric Asthma.

2005 Chair, American Thoracic Society International Conference Symposium: Health Disparities: Understanding and Addressing Them through Research and Practice.

Chair, American Thoracic Society International Conference Symposium: Implementation of Asthma Severity Measurements in the Real World of Clinical Practice: What Are We Doing Now and What Should Come Next?

2006 Chair, American Thoracic Society International Conference Symposium: The Complex Interaction of Race, Stress and Neighborhood on Respiratory Disease. May 21, 2006.

2007 Chair, American Thoracic Society International Conference Symposium: Current Methods for the Respiratory and Environmental Researcher: A Toolkit for Clinical Investigation

Chair, American Thoracic Society International Conference Symposium: Scientific Writing: How to Publish for Academic Success.

Chair, American Thoracic Society International Conference: Assembly on Behavioral Science Membership Meeting.

2008 Chair, American Thoracic Society International Conference Symposium: Introduction to Data Analysis: Exploring the Great Unknown.

Chair, American Thoracic Society International Conference Symposium: Asthma Severity Versus Asthma Control: What Should We Use in Clinical Practice?

- 2009 Chair, American Thoracic Society International Conference Symposium: Measuring and Improving the Quality of Care in Lung Disease.
- Facilitator, American Thoracic Society International Conference Symposium: Developing Surveys that Measure or Predict.
- Facilitator, American Thoracic Society International Conference Symposium: Asthma in the Inner City: A Unique Mix of Allergen and Pollutant Exposures.
- 2010 Chair, American Thoracic Society International Conference, Poster Session Discussion, New Orleans
- Chair, American Thoracic Society International Conference, Scientific Symposium: Individual susceptibility to air pollution.
- Chair, American Thoracic Society International Conference, Scientific Symposium: Asthma disparities: Root causes and global solution
- 2013 Chair, American Thoracic Society International Conference, EOH Program Committee
- 2013 Chair/Moderator, American Thoracic Society International Conference, Poster Session Discussion, Pollution Effects, Philadelphia
- 2013 Discussant, American Thoracic Society International Conference, Poster Session Discussion, Obesity: Impact on lung function and disease, Philadelphia
- 2013 Chair, Scientific Symposium: Developmental origins of asthma and allergies: Environment, modifiers and mediators, American Thoracic Society International Meeting, Philadelphia, May 2013.
- 2015 Chair, Scientific Symposium: Advances in Understanding and Reducing Asthma Disparities, American Thoracic Society International Meeting, San Diego, May 2015.

#### **Advisory Committees, Review Groups**

- 2001-2006 American Lung Association  
Member, National Grants Review Award Selection Committee
- 2002 American Healthways/Johns Hopkins 2nd Annual Disease Management Outcomes Summit: Standard Outcome Metrics and Evaluation Methodology for Disease Management Programs, November 7-10, 2002, Palm Desert, CA, Role: Physician Steering Committee
- 2003 American Healthways/Johns Hopkins 3<sup>rd</sup> Annual Disease Management Outcomes Summit: Defining the Patient-Physician Relationship for the 21<sup>st</sup> Century, October, 2003, Phoenix, AZ. Role: Physician Steering Committee
- Member, Aventis AVE0547 HE Asthma Advisory Board

- 2004 American Healthways/Johns Hopkins 4<sup>th</sup> Annual Disease Management Outcomes Summit: Outcomes-Based Compensation: Pay-for-Performance Design Principles, November 11-14, 2004, Rancho Mirage, CA, Role: Physician Steering Committee
- Member, DEY, LP, Managed Care Advisory Board, Napa, CA.
- 2005 American Healthways/Johns Hopkins 5<sup>th</sup> Annual Disease Management Outcomes Summit: Improving Care Coordination through Physician-Disease Management Collaboration, November 10-13, 2005, Fort Lauderdale, Florida, Role: Physician Steering Committee
- Invited Faculty representing ATS, National Workshop to Reduce Asthma Disparities, Chicago, Illinois
- 2006 American Healthways/Johns Hopkins 6<sup>th</sup> Annual Disease Management Outcomes Summit: Embracing Health: Tools and Systems for Health Promotion and Disease Prevention, November, 2006, JW Marriott Starr Pass Resort, Tucson, AZ , Role: Physician Steering Committee
- Member, NIH/NHLBI Grant Review Award Selection Committee
- Member, NHLBI Strategic Planning Process Committee
- 2007 American Healthways/Johns Hopkins 7<sup>th</sup> Annual Disease Management Outcomes Summit: Integrated Medicine: Complementary Approaches, November 8-11, 2007, Austin, Texas, Role: Physician Steering Committee
- 2008 Reviewer, *ad hoc*, Deutsche Forschungsgemeinschaft (German Research Foundation).
- Member, Cancer, Cardiovascular and Pulmonary Disease (CCPD) program. The Amendment 25 Program Evaluation Group.
- Member, National Committee for Quality Assurance (NCQA) Advisory Panel. HEDIS Trends Publication Expert Advisory Panel.
- 2008- Member, EXPORT's P60 Advisory Board, University of Puerto Rico (UPR)/CHA Research presentCenter of Excellence: Making a Difference for Latino Health. San Juan, Puerto Rico.
- 2008-2009 Chair, The Donaghue Program for Research Leadership, Hartford, CT.
- 2009-2011 Member, NIH/NHLBI Study Section for Patient Oriented Research (K23, 24, and 25).
- 2009 Member, NIH/NIAID Review Panel for Special Emphasis Study Section ZAI1-RRS-I-M1.
- 2010 Discussant, NIH/NIAID, Asthma, Allergy and Inflammation Branch: Asthma Outcomes Workshop, Bethesda, MD.
- 2011 Member, NIH/NHLBI Review Panel for Small Business Respiratory Sciences, Special Emphasis Study Section, ZRG1 CVRS-H (10) B (K12)

- 2011 Member, NIH/NHLBI Review Panel for NHLBI Career Development Programs in Emergency Medicine Research (K12).
- 2011 Chair, NIH/NHLBI Review Panel for RFA-HL-12-011, Development and testing of a case finding methodology in COPD (R01), Washington, DC
- 2012 Discussant, Webinar Presentation, NIEHS, Virtual Forum: Childhood Obesity and the Environment, November 2012. Research Triangle Park, NC

## **Consultancies**

Aventis 2002; Physician Advisory Panel

Cardiocontinuum, 1999-2000; Role: Development of COPD Program

American Healthways, 2002-Present; Role: Steering Committee Member and Performance Measure Development

Sorption Technologies, Inc., 2004-Present; Role: Research Design Consultant

Interactive Forums, Inc., 2004-Present; Role: Health Care Consulting

Merck, Beta-agonist Measure Panel Meeting, December 3, 2004, Denver, Colorado.

Pfizer Academic Round Table, May 24-25, 2005, American Thoracic Society, San Diego, California.

## **RECOGNITION**

### **Awards, honors**

1986 English Degree awarded with Honors, University of Pennsylvania

1986 BA, *Magna cum Laude*, University of Pennsylvania

1986 BS, *Magna cum Laude*, University of Pennsylvania

1997 Delta Omega Public Health Honor Society

2000 Solo Cup Clinician Scientist Award

2001 GlaxoSmithKline Development Partners' Junior Faculty Award

2009 Qforma's List of Most Influential Doctors, created for USA Today.

2010 Pfizer Visiting Professorship in Pulmonology.  
East Tennessee State University College of Public Health.

**Invited Talks, Panels**

- 1993 The Special Value of Undergraduate Research. Presented at the 64th Annual Meeting of the Eastern Psychological Association. Arlington, Virginia.
- PSA as a Screening Test? Medical Management Conference. Department of Internal Medicine, University of Pennsylvania.
- 1994 Carbon Monoxide Poisoning, Medical Management Conference, Department of Internal Medicine, University of Pennsylvania.
- Invited Discussant, Morbidity and Mortality Conference, Department of Internal Medicine, University of Pennsylvania.
- 1996 Vitamins and the Risk of Lung Cancer: Randomized Clinical Trials as a Gold-Standard, Longcope Attending Rounds, Department of Internal Medicine, The Johns Hopkins University School of Medicine.
- PSA and DRE Screening for Prostate Cancer: Principles of Screening, Longcope Attending Rounds, Department of Internal Medicine, Johns Hopkins University School of Medicine.
- 1997 Predictors of overuse of inhaled  $\beta$ -agonists, underuse of inhaled corticosteroids, and of nocturnal symptoms in adult asthmatics. Outcomes research group, Merck & Co., Inc., West Point, PA.
- Associations of misuse of asthma medications in adult asthmatics enrolled in managed care. Managed Care Health Care Consortium, Washington, DC.
- Misuse of corticosteroid and  $\beta$ -agonist metered dose inhalers (MDIs) among adult asthmatics in managed care (MCOs), Maryland Thoracic Society Annual Research Dinner, Baltimore, MD.
- 1998 Treatment patterns among adult asthmatics: Overuse of inhaled beta-agonists, underuse of inhaled corticosteroids, Division of Pulmonary and Critical Care Medicine, Yale University School of Medicine, New Haven, CT.
- Treatment patterns among adult asthmatics: Overuse of inhaled beta-agonists, underuse of inhaled corticosteroids, Division of General Internal Medicine, Case Western University School of Medicine, Cleveland, OH.
- Misuse of corticosteroid and  $\beta$ -agonist metered dose inhalers (MDIs) among adult asthmatics in managed care (MCOs), Combined Allergy and Immunology Meeting, Palm Beach, FL.
- Future HEDIS Measures for Asthma. Glaxo-Wellcome Asthma Managed Care Consultants Program. Naples, FL.
- Asthma Therapy Assessment Questionnaire: Results of a Validation Study, Blue Plus, Minneapolis, MN.
- 1999 Bronchoscopy Quality Improvement Project: A Hospital Based Cohort Study. Health Services Research and Development Research Seminar.

Lesson Learned from Studies of Asthma in Managed Care. Best Practices Symposium sponsored by the Pacific Business Group on Health, Oakland, California.

Quality of Care and Guidelines: Management of Asthma. Practice Guidelines Workshop. Johns Hopkins Medical Services Corporation, Baltimore, MD, November 1999 and May 2000.

- 2000 Asthma Care by Asthma Specialists. Department of Medicine Grand Rounds. Greater Baltimore Medical Center, Baltimore, MD.

Predictors of Outcomes in Asthma. Frontiers in Research and Clinical Management of Asthma and Allergy Conference. Johns Hopkins Asthma & Allergy Center, Baltimore, MD.

Update in Asthma. Update in Pulmonary and Critical Care Medicine, Johns Hopkins University, Santa Fe, NM.

Fine-tuning your Bronchoscopy Practice. Bronchoscopy Workshop. Johns Hopkins University, Santa Fe, NM.

Underuse of Inhaled Corticosteroids in Asthma. Department of Medicine Grand Rounds, Johns Hopkins University, Baltimore, MD.

Nocturnal Asthma: Impact on Children and Their Parents. Research Conference of the Center for Childhood Asthma in the Urban Environment, Johns Hopkins University, Baltimore, MD.

Bronchoscopy Quality Improvement Project: Design Issues and Results. Robert Wood Johnson Clinical Scholars Program, Johns Hopkins University, February 1998 and April 2000.

- 2001 COPD- The Role of Steroids. Maryland Thoracic Society 41<sup>st</sup> Annual Meeting and Scientific Session, Pulmonary and Critical Care Medicine: State-of-the-Art, Baltimore, MD.

Update in Asthma. Johns Hopkins Bayview Medical Center, Department of Medicine, Baltimore, MD.

Severity, Control and Nocturnal Symptoms of Asthma in Children. Research Conference, Division of Pediatric Pulmonary Medicine, Johns Hopkins University. Baltimore, MD.

- 2002 Non-pharmacologic pain control with Bedscapes for Bronchoscopy. American Red Cross, Arlington, VA.

- 2003 Annual High Sierra Critical Care Conference; Update in Asthma Management for 2003.

Annual High Sierra Critical Care Conference; How to get the most from your bronchoscopy practice.

Office of Community Health, Community Chats 2002-2003.

Burnt Pizza and Near-Death from Asthma. Department of Internal Medicine Grand Rounds, Johns Hopkins Bayview Medical Center, Baltimore, Maryland.

Using Functional Genomics to Understand Complex Lung Disease, ATS/NHLBI.

Aligning Asthma Care with Assessment of Severity, Healthcare Quality and Safety Research Seminar Series, JHU.

Asthma Epidemiology, World Allergy Organization (WAO), Vancouver.

Aligning Asthma Care with Assessment of Severity. Pulmonary and Critical Care Grand Rounds, Oregon Health Services University.

- 2004 Office of Community Health, Community Chats 2003-2004; Impact of Night Time Asthma on Children and their Families Effective Asthma Medication.

The Role of the Indoor Home Environment in Childhood Asthma. Johns Hopkins-Barbados Genetic Epidemiology of Obstructive Lung Disease Research Conference, Almond Bay, Hastings, Christ Church, Barbados.

Environmental Factors Impacting Respiratory and Immunologic Disease. Gulf Coast Pediatric Environmental Health Symposium, Baylor College of Medicine, Houston, Texas.

Aligning Asthma Care with Estimates of Asthma Severity: Development of the Asthma Communication Instrument. Research Conference, Division of Pulmonary and Critical Care Medicine, Department of Pediatrics, Johns Hopkins University, Baltimore, Maryland.

Epidemiology as a Tool for Understanding Respiratory Disease: Case-Control Studies, American Thoracic Society, Orlando, Florida.

Standardizing the Care of the Patient with COPD: Is the Quality of Care Truly Improved? American Thoracic Society, Orlando, Florida.

Getting the Most Out of Bronchoscopy Services, 6<sup>th</sup> Annual Update, Pulmonary and Critical Care Medicine, Santa Rosa, California.

Severe Asthma: Current and Future Management, 6<sup>th</sup> Annual Update, Pulmonary and Critical Care Medicine, Santa Rosa, California.

- 2005 Office of Community Health, Community Chats 2005-2006. The Growing Child and Other Health Issues: Impact of Night-Time Asthma on Children and Their Families

Office of Community Health, Community Chats 2005-2006; Lung Disease: Making the Home Safer for Asthmatics.

Health Care Communications and Cultural Competency, National Workshop to Reduce Asthma Disparities, Chicago, Illinois.

The Home Environment of East Baltimore Preschool Children With and Without Asthma, Department of Physiology, Bloomberg School of Public Health, Johns Hopkins University.

COPD: A Pragmatic Approach to Improving Outcomes. Baltimore, Maryland.

COPD: A Pragmatic Approach to Improving Outcomes. COPD Exchange, Pittsburgh, Pennsylvania.

COPD: Evolving Concepts of Therapy. COPD Exchange, Baltimore, Maryland.

Aligning Asthma Care with Assessment of Severity and Control in Practice. Department of Internal Medicine, York Hospital, York, Pennsylvania.

Office of Community Health, Community Chats 2005-2006; Treating Asthma in Children, New Psalmist Christian School, Baltimore, Maryland.

The Role of the Indoor Home Environment in Childhood Asthma. Johns Hopkins-Barbados Asthma Conference, Almond Bay, Hastings, Christ Church, Barbados.

Is it Smart to Prescribe Long-Acting  $\beta$ -Agonists for Patients with Asthma? Division of Allergy and Clinical Immunology, Johns Hopkins University. December 2, 2005; and Rush University, Chicago, Illinois.

Aligning Asthma Care with Assessment of Severity and Control in Practice. Primary Care Conference, Baltimore, Maryland, February 24, 2006; Ohio State Pulmonary Grand Rounds, April 7, 2006; and Hospital of the University of Pennsylvania. January 25, 2008.

2006 Aligning Asthma Care with Assessment of Severity and Control in Practice. American Lung Association, Chicago, Illinois.

Should We Still use Long-acting Beta-Agonists in Patients with Asthma? Johns Hopkins University, School of Medicine, Department of Medicine Grand Rounds.

Development of the Asthma and Control Communication Instrument. University of Maryland, Pulmonary Research Conference, Baltimore, MD.

Update in COPD. Baltimore-Washington Hospital, Department of Medicine Grand Rounds. Glen Burnie, Maryland.

Issues Related to Beta-2 Agonist Therapy; Polymorphisms/Clinical Outcomes/Adverse Events Profile. 20<sup>th</sup> Annual Update. Frontiers in Research and Clinical Management of Asthma and Allergy: From Bench to Bedside. Johns Hopkins University School of Medicine, Division of Allergy and Clinical Immunology, Johns Hopkins Asthma & Allergy Center at Johns Hopkins Bayview Medical Center, Baltimore, Maryland.

2007 Office of Community Health, Community Chats 2007-2008; Asthma: How Asthmatics Can Make Their Home Safer; Effective Asthma Medication.

Hyperinflation in COPD Linking Physiology to Patient Experience. Boehringer-Ingelheim Pharmaceuticals, Inc, Christiana Care Hospital, Newark, Delaware.

Environmental Issues in Managing Asthma. 41<sup>st</sup> Respiratory Care Journal Conference. Scottsdale, Arizona, September 28, 2007.

Translational Science Think Tank. Collaborative Research Bridging Basic, Clinical and Health Services Domains: Challenges and Opportunities.” University of Connecticut Health Center, Farmington, CT, December 6, 2007.

- 2008 NCQA On-line Program: Best Practices in COPD Treatment. Course Faculty. December 2007-December 2008.

Approaching and Garnering the Support of Community Partners for Community-Based Research. American Thoracic Society International Meeting.

Logistic Regression. American Thoracic Society International Meeting Post-graduate Course.

Assessing Control is Good, But Not Sufficient for Management of Asthma. American Thoracic Society International Meeting Scientific Symposium.

The Death of Primary Care. Barker Grand Rounds, Johns Hopkins University, Baltimore, Maryland.

Is Genetic Polymorphism important in response to asthma therapy? Johns Hopkins 21<sup>st</sup> Update Frontiers in Research and Clinical Management of Asthma and Allergy. Johns Hopkins Asthma and Allergy Center, Baltimore, Maryland.

Joint Indo-US Workshop on Environmental Risks of Respiratory Disease. Prevalence of Respiratory Disease in India. Chandigarh, India.

Bridging the Evidence-to-Practice Gap in Asthma and Chronic Obstructive Pulmonary Disease from a National and International Perspective: An Update. American Thoracic Society International Meeting, San Diego, CA.

- 2009 Diet and inner city asthma: Is there a connection? Department of Medicine Grand Rounds, Johns Hopkins University, Baltimore, MD.

Role of indoor pollutants in respiratory disease. Fellows Orientation Conference, Division of Allergy and Clinical Immunology, Johns Hopkins University, Baltimore, MD.

Susceptibility determinants of childhood asthma. Session: Contributing factors that influence the relationship between environmental exposures and children’s health. Pediatric Academic Societies Annual Meeting, Baltimore, MD.

Scientific Advisory Committee, Merck Childhood Asthma Network, Washington, DC.

Pediatric Asthma Roundtable meeting-Improve lives of children with asthma in the Baltimore area. National Asthma Campaign, Baltimore, MD.

- 2010 Topics in Clinical Medicine 2010. Session: Meet the Professor—Pulmonary. Johns Hopkins University Annual Topics in Clinical Medicine, Baltimore, MD.

Validated questionnaires in the management of allergic disorders: Applications and interpretation. Johns Hopkins Community Physicians, Baltimore, MD.

Validated questionnaires in the management of allergic disorders: Effective Use in an Allergy Practice Setting. Session: State-of-the-Art Session 2525: American Academy of Allergy, Asthma and Immunology International Meeting, New Orleans, LA.

Indoor environmental exposures and asthma disparities. Scientific Symposium: Asthma disparities: Root cause and global solution. American Thoracic Society International Meeting, New Orleans, LA.

- 2010 Speaker: Environmental Issues in Managing Asthma. Post-Graduate Respiratory Medicine Meeting, Irish Lung Foundation, Dublin, Ireland. June 2010.

Speaker, Asthma Update Seminar. Eastern Shore AHEC, Hyatt Regency Chesapeake Bay, Cambridge, Maryland. August 2010.

Academy of Industrial Hygiene, PCIH 2010. Fort Worth, Texas, October 7-8, 2010  
21<sup>st</sup> Century Toxicity Testing and Human Health Risk Assessment for Environmental Agents.

Speaker: (1) "Lung responses to environmental toxins"

Speaker: (2) "Environmental residential exposures to allergens and irritant gases"

Speaker: (3) "Role of Pulmonary and Respiratory Irritants in Asthma, COPD, and Bronchiolitis Obliterans"

Speaker: "Is diet driving the asthma epidemic?" NIEHS/EPA Conference, Protecting children's health for a lifetime: Environmental health research meets clinical practice and public policy conference, October 19-20, Washington, DC

Speaker: Environmental Health Department Doctoral Seminar, Boston University, October 22, 2010. "The role of indoor pollutants and allergens and asthma in inner city children: Some of the bad ingredients in a toxic stew."

Participant, Workshop: Task Force for the Asthma Disparities Working Group/Federal Task Force on Environmental Health Risks and Safety Risks to Children Steering Committee, "Developing a coordinated federal action plan to reduce asthma disparities." NIH-NHLBI/EPA/HUD. Washington, DC. December 16-17, 2010.

- 2011 Visiting Professor, Leading Voices in Public Health Lecture Series. "The mouse, the house and the hamburger: Making sense of the asthma epidemic." The College of Public Health and the Public Health Student Association, East Tennessee State University, March 3, 2011.

Lecturer, Teaching Course entitled Health Care Organization and Delivery: "Indoor environmental exposures and asthma disparities." East Tennessee State University, March 3, 2011.

Lecturer, Teaching Course entitled Introduction to Air Pollution: "Asthma and Air Pollution." East Tennessee State University, March 4, 2011.

Invited Speaker: U.S. Congress Briefing, Preventing Breast Cancer and Pediatric Asthma: Links to the Environments of Women and Children, Rayburn House Office Building B-354 NIH/NIEHS. "The Mouse, the House and the Hamburger: Making Sense of the Asthma Epidemic." April 21, 2011.

Invited Speaker-Panelist: Clearing the Air, Addressing asthma disparities in Maryland.  
Session A-3: “Asthma Interventions: Research into Practice,” and  
Session B-4: “The human side of asthma: Educating patients to make health decisions—overcoming barriers to medication adherence.” Linthicum, MD. June 2011.

Invited Speaker: National Healthy Homes Conference. Track 7: Just the Facts. Session 7H-2.  
“Nanoparticles and nitrogen dioxide from stoves: Health effects and strategies to reduce exposure and improve asthma control.” Denver, CO. June 2011.

- 2012 Visiting Professor, Division of Pulmonary Medicine, Allergy and Immunology Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA, January 5, 2012.

Invited Speaker, Pediatric Pharmacology Division, National Jewish Health. “The house, the mouse and the hamburger: Making sense of the asthma epidemic.” Denver, CO, June 2012.

Invited Speaker, Johns Hopkins Bloomberg School of Public Health/The Maryland Department of Health and Mental Hygiene/The mid-Atlantic Public Health Training Center. “Reducing asthma disparities in children: A model program with promising results. Baltimore, MD, June 2012.

Invited Speaker, EPA/NIEHS Children’s Centers 2012 Webinar Series, Protecting children’s health for a lifetime. “Role of home environment and diet on childhood asthma.” December 2012.

- 2013 Visiting Professor, “The house, the mouse and pizza: Explaining the asthma epidemic.” Universidad de Los Andes, Bogota, Columbia, April 2013.

Invited Speaker, Scientific Symposium: Developmental origins of asthma and allergies: Environment, modifiers and mediators, “Indoor exposures and ETS.” American Thoracic Society International Meeting, Philadelphia, PA. May 2013.

Invited Speaker, Congressional Briefing, Health and Medicine Counsel of Washington. “Protecting children’s health for a lifetime: How the environment influences health and development,” hosted by Senator Kirsten E. Gillibrand, 385 Russell Senate Office Building. Sponsored by Friends of NIEHS, the American Academy of Pediatrics, and the Children’s Environmental Health Network. October 2013.

Invited Lecturer, Johns Hopkins University School of Nursing, “Diagnosis, Symptom, and Illness Management I – Adult Course.” Topic: Asthma. December 2013.

- 2014 Invited Lecturer and participant, NIH – MOST Clinical and Translational Science Workshop, NIH Campus, Stone House, Bethesda, MD, July 21-22, 2014.

Invited Speaker, Respiratory Expert Forum Ireland, “Beat the Professor” Case Studies on treating difficult airways disease, Dublin, Ireland, October 17-18, 2014.

- 2015 Invited Speaker, The Children’s Environmental Health Network’s 2015 CEHN Pediatric Research Conference Children: Food and Environment, “Prevention and Treatment of Asthma with Diet: Progress and Promise.” The University of Texas at Austin, Austin, TX. February 4-6, 2015.

Invited Speaker, Scientific Symposium: Advances in Understanding and Reducing Asthma Disparities, “Indoor Exposures and Asthma Disparities.” American Thoracic Society International Meeting, San Diego, CA. May 2015.

Office of Community Health, Community Chats 2015-2016; Asthma: “How People With Asthma Can Make Their Homes Safer.”

Office of Community Health, Community Chats 2015-2016; Asthma: “Does Diet Affect Asthma?”

# APPENDIX D

Gregory Diette, MD, MHS

Diette publications, continued, after June 2017

1. Brigham EP, Steffen LM, London SJ, Boyce D, **Diette GB**, Hansel NN, Rice J, McCormack MC. Diet Pattern and Respiratory Morbidity in the Atherosclerosis Risk in Communities Study. *Annals of the American Thoracic Society*. 2018; 15(6).
2. Brigham EP, Matsui EC, Appel LJ, Bull DA, Curtin-Brosnan J, Zhai S, White K, Charleston JB, Hansel NN, **Diette GB**, McCormack MC. A pilot feeding study for adults with asthma: The healthy eating better breathing trial. *PLOS ONE*. 2017; 12(7).
3. Cloutier MM, Salo PM, Akinbami LJ, Cohn RD, Wilkerson JC, **Diette GB**, Williams S, Elward KS, Mazurek JM, Spinner JR, Mitchell TA, Zeldin DC. Clinician Agreement, Self-Efficacy, and Adherence with the Guidelines for the Diagnosis and Management of Asthma. *The Journal of Allergy and Clinical Immunology: In Practice*. 2018; 6(3): 886-894.
4. Lin SY, Azar A, Suarez -Cuervo C, **Diette GB**, Brigham E, Rice J, Ramanathan M, Gayleard J, Robinson KA. The Role of Immunotherapy in the Treatment of Asthma. *AHRQ Comparative Effectiveness Reviews*, No. 196. 2018.
5. Lin SY, Azar A, Suarez-Cuervo C, **Diette GB**, Brigham E, Rice J, Ramanathan Jr. M, Robinson KA. Role of sublingual immunotherapy in the treatment of asthma: An updated systematic review. *International Forum of Allergy and Rhinology*. 2018; 8(9): 982-992.
6. McCormack MC, Paulin LM, Gummerson CE, Peng RD, **Diette GB**, Hansel NN. Colder temperature is associated with increased COPD morbidity. *European Respiratory Journal*. 2017; 49(6).
7. Nnodum BN, McCormack MC, Putcha N, Hwang S, Paulin LM, Brigham EP, Fawzy A, Romero K, **Diette GB**, Hansel NN. Impact of Physical Activity on Reporting of Childhood Asthma Symptoms. *Lung*. 2017; 195(6): 693-698.
8. Paulin LM, Williams DL, Peng R, **Diette GB**, McCormack MC, Breysse P, Hansel NN. 24-h Nitrogen dioxide concentration is associated with cooking behaviors and an increase in rescue medication use in children with asthma. *Environmental Research*. 2017; 159: 118-213.
9. Rice JL, **Diette GB**, Suarez-Cuervo C, Brigham EP, Lin SY, Ramanathan Jr. M, Robinson KA, Azar A. Allergen-Specific Immunotherapy in the Treatment of Pediatric Asthma: A Systematic Review. *Pediatrics*. 2018; 141(5).
10. Rice JL, Brigham E, Dineen R, Muqueeth S, O'Keefe G, Regenold S, Koehler K, Rule A, McCormack M, Hansel NN, **Diette GB**. The feasibility of an air purifier and secondhand smoke education intervention in homes of inner city pregnant women and infants living with a smoker. *Environmental Research*. 2018; 160: 524-530.
11. Sulaiman I, Greene G, MacHale E, Seheult J, Mokoka M, D'Arcy S, Taylor T, Murphy DM, Hunt E, Lane SJ, **Diette GB**, FitzGerald JM, Boland F, Bhreathnach AS, Cushen B, Reilly RB, Doyle F, Costello RW. A randomized clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma. *European Respiratory Journal*. 2018; 51(1).

Gregory Diette, MD, MHS

Diette publications, continued, after June 2017

12. Wu TD, Eakin MN, Rand CS, Brigham EP, **Diette GB**, Hansel NN, McCormack MC. In-Home Secondhand Smoke Exposure Among Urban Children With Asthma: Contrasting Households With and Without Residential Smokers. *Journal of Public Health Management and Practice*. 2018; 25(2): E7-E16.
13. Wu TD, Brigham EP, Peng R, Koehler K, Rand C, Matsui EC, **Diette GB**, Hansel NN, McCormack MC. Overweight/obesity enhances associations between secondhand smoke exposure and asthma morbidity in children. *The Journal of Allergy and Clinical Immunology: In Practice*. 2018; 6(6): 2157-2159.
14. POSTER DISCUSSION SESSION:  
  
Nnodum BN, Hwang S, Romero K, Kineza C, Tariq Z, Peng R, Putcha N, McCormack MC, Diette GB, Hansel NN. Impact Of Physical Activity On Childhood Asthma Symptoms: Longitudinal Study In Inner City Baltimore, Maryland. *Poster Discussion Session/ Wednesday May 24 2017/ Walter E. Washington Convention Center*
15. POSTER DISCUSSION SESSION:  
  
Wu TD, Eakin M, Rand CS, Brigham E, Diette GB, Hansel NN, McCormack MC. Factors Associated with In-Home Secondhand Smoke Exposure from External Sources in Urban Children with Asthma. *Poster Discussion Session/ Sunday May 20/ San Diego Convention Center*
16. POSTER DISCUSSION SESSION:  
  
Wu TD, Brigham E, Rand CS, **Diette GB**, Peng R, Putcha N, Koehler K, Hansel NN, McCormack MC. Overweight and Obesity Increases Respiratory Symptoms Associated With Secondhand Smoke Exposure Among Us Children. *Poster Discussion Session/ Wednesday May 24/ Walter E. Washington Convention Center*
17. POSTER DISCUSSION SESSION:  
  
Koch A, Woo H, Brown RH, Brooker A, Paulin LM, Schneider H, Schwartz AR, Diette GB, Wise RA, Hansel NN, Putcha N. Obstructive Sleep Apnea is Associated with Airway Dimensions in COPD. *Poster Discussion Session/ Tuesday May 22, 2018/ Marriott Marquis San Diego Marina*
18. POSTER DISCUSSION SESSION:  
  
Liesching TN, Huynh T, Cereda M, **Diette GB**. Treatment with the MetaNeb® System in High-Risk Post-Surgical Patients Reduced Hospital and Intensive Care Unit Length of Stay. *Poster Discussion Session/Sunday May 20/San Diego Convention Center*
19. POSTER DISCUSSION SESSION:  
  
Polito C, Eakin M, Woo H, Romero K, McCormack MC, Fawzy A, Paulin LM, **Diette GB**, Koehler K, Hansel NN, Putcha N. Indoor Air Pollution May Be Associated with cognitive Impairment in Chronic Obstructive Pulmonary Disease. *Thematic Discussion Session/Monday May 21/San Diego Convention Center*
20. POSTER DISCUSSION SESSION:

Gregory Diette, MD, MHS

Diette publications, continued, after June 2017

Putchá N, Fawzy A, Matsui E, Bowler RP, Woodruff P, O'Neal WK, Comellas AP, Han MK, Dransfield MT, Lugogo N, Hoffman EA, Cooper CB, Hersh CP, Paulin LM, Drummond M, Wise RA, **Diette GB**, Hansel NN. Allergen Sensitization and Exposure Is Associated with Exacerbations in COPD. *Poster Discussion Session/Monday May 21/San Diego Convention Center*

21. POSTER DISCUSSION SESSION

Rice J, Brigham EP, Koehler K, McCormack MC, **Diette GB**, Woo H, Hanson C, Sharma S, Kolahdooz F, Hansel NN. Adherence to a Mediterranean Diet Attenuates the Adverse Effect of Indoor Particulate Matter on Asthma Symptoms in Children. *Poster Discussion Session/ Tuesday May 22/ San Diego Convention Center*

22. THEMATIC POSTER SESSION:

Wu TD, Rice J, Koehl R, Brigham E, **Diette GB**, Hansel NN, Sterni LM, McCormack MC. Pediatric Sleep Disordered Breathing is Associated with Worse Acute Asthma Control. *Thematic Poster Session/ Sunday May 20, 2018/ San Diego Convention Center*

23. THEMATIC POSTER SESSION:

Cereda M, Huynh T, Liesching T, **Diette GB**. Identification Of Surgical Population At High Risk Of Postoperative Pulmonary Complications. *Thematic Poster Session/ Sunday May 21, 2017/ Walter E, Washington Convention Center*

24. THEMATIC POSTER SESSION:

Soto, CML, Woo H, Romero K, Brigham E, McCormack MC, **Diette GB**, Hanson C, Fawzy A, Koch A, Putcha N, Hansel NN. Association of Omega-3 and Omega-6 Fatty Acid Intake with Inflammation and Respiratory Outcomes in COPD. *Thematic Poster Session/ Monday May 21, 2018/ San Diego Convention Center*

25. MINI SYMPOSIUM:

Bose S, McCormack MC, Woo HS, Romero K, Brigham E, Koehler K, Detrick B, **Diette GB**, Hansel NN. Vitamin D Status Modifies Response to Indoor Air Pollution in Urban Children with Asthma. *Mini Symposium/ Sunday May 20/ San Diego Convention Center*

26. MINI SYMPOSIUM:

Brigham E, McCormack MC, Woo H, Rice J, Koehler K, Vulcain T, Wu TD, Biswal SS, Sudini K, Koch A, Hanson C, Sangita S, Kolahdooz F, Bose S, Romero K, **Diette GB**, Hansel NN. Omega-3 and Omega-6 Fatty Acid Intake Modifies Response to Indoor Air Pollution in Children with Asthma. *Mini Symposium/ Sunday May 20/ San Diego Convention Center.*

27. Listed as a Reviewer and Technical Contributor:

World Health Organization. Air Pollution and Child Health: Prescribing Clean Air Summary. 2018.

# APPENDIX E

Date	Case Name	Case Number	Deposition or Trial
16-Jan-2014	Ismael Rosas v. Flavorchem Corporation, et al	Superior Court of the State of California Count of Los Angeles, Central Civil West Case No.: BC400974	Deposition (O'Laughlin Industries)
1-Aug-2014	Tanu Vatuvei v. Mission Flavors & Fragrances, Inc., et al.	Superior Court of the State of California for the county of Orange, Central Justice Center Case No.: 30-2011-00518123	Deposition (O'Laughlin Industries)
10-Jun-2014	Harry Goldsmith v. ACandS, Inc., et al. (Law Offices of Peter G. Angelos: Mr. William Minkin, Esq.)	In the Circuit Court for Baltimore City Case No.: 24x13000097	Deposition (Hampshire Industries)
3-Oct-2014	Charles Waters v. ACandS, Inc., et al. (Law Offices of Peter G. Angelos: Mr. Gary Ignatowski, Esq.)	In the Circuit Court for Baltimore City Case No.: 24x13000461	Deposition (Hampshire Industries)
31-Oct-2014	Francis Murphy v. ACandS, Inc., et al. (Law Offices of Peter G. Angelos: Mr. William Minkin, Esq.)	In the Circuit Court for Baltimore City Case No.: 24x13000371	Deposition (Hampshire Industries)
19-Feb-2015	Rachele and David Ventres v. 002 Auto Parts Inc., et al. (Levy Konigsberg: Joseph Mandia, Esq.)	Superior Court of New Jersey Case No.: MID-L-1933-12AS	Deposition (BASF)
19-Feb-2015	Thomas and Donna Gioglio v. 3M Company, et al. (Levy Konigsberg: Joseph Mandia, Esq.)	Superior Court of New Jersey Case No.: MID-L-4593-12AS	Deposition (BASF)
25-Feb-2015	Lorene McKenzie, deceased v. Palestine Principal Healthcare Limited Partnership, et al.	District Court of Anderson County Texas, 369th Judicial District. Case No.: 369-12-4684	Trial (Plaintiff)
13-Mar-2015	Walter Henry Hakenjos v. AT&T Corporation, et al. (Cannella Law Firm: David Cannella, Esq.)	Civil District Court for the Parish of Orleans State of Louisiana Case No.: 14-3828	Deposition (AT&T)
10-Apr-2015	Robert Menoche (as part of Raymond Michaels, et al.) v. ACandS, Inc., et al. (Law Offices of Peter G. Angelos: Mr. Theodore Fierlage, Jr., Esq.)	In the Circuit Court for Baltimore City Case No.: 24x14000259	Deposition (Hampshire Industries)

Date	Case Name	Case Number	Deposition or Trial
22-May-2015	Kathy Mason v. Vistas at Lake Largo, LLC (Eccleston and Wolf: Mark Johnson, Esq.)		Deposition (de bene esse) (Vistas at Lake Largo)
3-Jun-2015	Senate Committee on Environment & Public Works	Challenges and Implications of EPA's Proposed National Ambient Air Quality Standard for Ground-Level Ozone and Legislative Hearing on S. 638, S. 751, and S. 640.	(Minority)
12-Jun-2015	Donald Russ and Ann Russ v. Alcatel-Lucent USA Inc, et al. (Simmons Hanley Conroy: Daniel Blouin, Esq.)	In the Superior Court of New Jersey Case No.: MID-L-1249-14-AS	Deposition (AT&T)
16-Jun-2015	House Committee on Energy & Commerce	EPA's Proposed Ozone Rule: Potential Impacts on Manufacturing.	(Minority)
31-Jul-2015	Eric Heggie, as Special Administrator of the Estate of Karry Heggie, Deceased v. Honeywell International, Inc., Et al. (Wylder Corwin Kelly LLP)	In the Circuit Court of the Eleventh Judicial Circuit County of McLean Case No.: 12 L 87	Deposition (Lincoln Electric Company; Hobart Brothers Company)
23-Oct-2015	Kris Penny v. AT&T Corporation, et al. (The Ruckdeschel Law Firm, LLC)	In the United States District Court Middle District of Florida Orlando Division Case No.: 6:15-cv-557-ORL-31KRS	Deposition (AT&T)
25-Aug-2016	Wanda Allen, Individually and as Personal Representative of the Estate of Byron K. Allen, et al. (Dumer & Barnes, P.A.)	In the Circuit Court for Baltimore City Case No.: 24-C-15-003256 OT	Deposition (Clinical Associates, PA: Sinai Hospital of Baltimore, Inc.)
28-Sep-2016	Rudiger & Joan Herion v. Donley's Inc., et al. (Bevan & Associates LPA, Inc.)	In the Court of Common Pleas, Cuyahoga County, Ohio Case No.: 15 CV 848879	Deposition (Donley's Inc.)
11-Jan-2017	Anita M. Albright v. Kevin Anthony Seymour (Law Office of Neil J. Bixler, P.A.: Neil Bixler, Esq.)	Carroll County Circuit Court in Maryland	Trial (Kevin Anthony Seymour)

Date	Case Name	Case Number	Deposition or Trial
3-Feb-2017	Brian Tucker and Sherri Tucker, his wife v. Momentive Performance Materials USA, Inc., et al. (Motley Rice, LLC: Scott B. Hall, Esq.)	In the United States District Court for the Southern District of West Virginia at Charleston Civil Action No. 2:13-cv-04480	Deposition (Joint Defense)
3-Mar-2017	Dennis John Zampa and Pamela S. Zampa v. Georgia-Pacific LLC, et al. (Kazan, McClain, Satterley & Greenwood: Trey Jones, Esq.)	In the Alameda County Superior Court of California Case No.: RG16836998	Deposition (E.I. Du Pont de Nemours and Company)
8-Mar-2017	Gregory Aregood, Jr., et al. v. International Flavors & Fragrances, Inc., et al. (Humphrey, Farrington & McClain, P.C.: Steven E. Crick, Esq.)	United States District Court for the Southern District of Indiana Civil Action No.: 1:14-CV-00274-LRM-TAB	Deposition (Givaudan Flavors Corporation)
24-Mar-2017	Gregory Aregood, Jr., et al. v. International Flavors & Fragrances, Inc., et al. (Humphrey, Farrington & McClain, P.C.: Steven E. Crick, Esq.)	United States District Court for the Southern District of Indiana Civil Action No.: 1:14-CV-00274-LRM-TAB	Continued Deposition (Givaudan Flavors Corporation)
29-Mar-2017	Dennis John Zampa and Pamela S. Zampa v. Georgia-Pacific LLC, et al. (Kazan, McClain, Satterley & Greenwood: Trey Jones, Esq.)	In the Alameda County Superior Court of California Case No.: RG16836998	Deposition (E.I. Du Pont de Nemours and Company)
6-Sep-2017	Aaron Ruby, et al., v. International Flavor & Fragrances, INC., et al. (Stephen J. Butler, Esq.)	Court of Common Pleas Marion County, Ohio Case No.: 2014 CV 0509	Deposition (Givaudan Flavors Corporation)
14-Dec-2017	Terry Darpel, et al. v. Cargill Flavor Systems US, LLC, et al. (Motley Rice, LLC: Scott B. Hall, Esq.)	Commonwealth of Kentucky Kenton Circuit Court, Division III. Case No.: 12-CI-446	Deposition (Emoral; Berje Incorporated)
17-Jan-2018	Delbert Cohen, Individually, and as Personal Representative of the Estate of Muriel Cohen, et al., v. 84 Lumber Company, et al. (The Ruckdeschel Law Firm, LLC; Z. Stephen Horvat, Esq.)	In the Circuit Court for Prince George's County Case No.: CAL16-37427	Deposition (Hampshire Industries)

Date	Case Name	Case Number	Deposition or Trial
4-Apr-2018	Darrell Palmer and Norma Palmer v. Appleton GRP, LLC d/b/a Appleton Group and Emerson Electric Co., et al. (George & Farinas, LLP)	In the Marion Superior Court SS: Civil Division Room 2 Cause No. 49D02-1704-MI-016728	Deposition (Rockwell Automation; Reliance Electric)
22-Apr-2018	Gail Lucille Ingham and Robert Ingham, et al. v. Johnson & Johnson; Johnson & Johnson Consumer Companies, Inc.; and Imerys Talc America, Inc., f/k/a Luzenac America, Inc. (The Lanier Law Firm; Sam E. Taylor, Esq.)	In the Circuit Court of the City of St. Louis State of Missouri Cause No. 1522-CC10417-01	Deposition (Johnson & Johnson)
10-Jul-2018	Blades, Kevin, et al. v. Emoral, Inc., f/k/a Polarome International, Inc., et al. (Humphrey, Farrington & McClain; Scott A. Britton-Mehlisch)	In the Circuit Court of Jasper County, Missouri Case No. 17AO-CC00025	Deposition (Emoral)
27-Jul-2018	Herman Leischner and Bonnie Leischner v. Aerco International, Inc., et al. (Wylde Corwin Kelly LLP; Stephen Wood, Esq.)	In the Circuit Court of the Eleventh Judicial Circuit County of McLean No. 15 L 53	Deposition (Hobart Brothers and Lincoln Electric)
3-Aug-2018	Marlin Herbst v. Bush Boake Allen, Inc., et al. (Humphrey, Farrington & McClain; Michael S. Kilgore, Esq.)	In the United States District Court Northern District of Iowa Western Division No. C17-4008-MWB	Deposition (Givaudan Flavors Corporation & Emoral, Inc.)
30-Aug-2018	Rosalind Henry and Frederick C. Henry v. Brenntag North America, et al. (Motley Rice LLC; W. Christopher Swett, Esq.)	Superior Court of New Jersey, Middlesex County No. MID-L-1748-17AS	Deposition (Johnson & Johnson, Johnson & Johnson Consumer Inc., and Imerys Talc America, Inc.)
28-Sep-2018	Nelcome Courville, Jr. v. Lamorak Insurance Company, et al. (Roussel & Clement; Gerolyn P. Roussel, Esq.)	Civil District Court for the Parish of New Orleans, Louisiana No. 2017-1117	Deposition (Chemours Company)

Date	Case Name	Case Number	Deposition or Trial
3-Oct-2018	Rosalind Henry and Frederick C. Henry v. Brenntag North America, et al. (Motley Rice LLC; W. Christopher Swett, Esq.)	Superior Court of New Jersey, Middlesex County No. MID-L-1748-17AS	Trial (Johnson & Johnson, Johnson & Johnson Consumer Inc., and Imerys Talc America, Inc.)
17-Oct-2018	Carol Kerkhof, et al. v. Brenntag North American, INC, et al. (Simon Greenstone Panatier Bartlett, PC)	Circuit Court for Montgomery County No. 439392-V	Deposition (Johnson & Johnson, Johnson & Johnson Consumer Inc., and Imerys Talc America, Inc.)
26-Oct-2018	Anastasia Brower, a minor, through her legal guardian Pamela Russell, and Pamela Russell, as the executrix of the Estate of Diane Brower, deceased v. Johnson & Johnson, et al.	In the State Court of Fulton County Fulton State of Georgia No. 16-EV-005534-E	Deposition (Johnson & Johnson, Johnson & Johnson Consumer Inc.)
9-Nov-2018	Paul E. Beach and Rheta E. Beach, Pltfs. vs. 3M Company, etc., et al.	Superior Court of the State of California, County of Alameda - Court of Unlimited Jurisdiction. Case No. RG18893273	Deposition (Rockwell Automation)
13-Dec-2018	Terry Lee Siegfried v. 3M Company, etc., et al. (The Lanier Law Firm; Mark A. Linder, Esq.)	Los Angeles County- Superior Court- Case No. BC691900	Deposition (Rockwell Automation)
9-Jan-2019	Joseph Woon-Shing Lee and Marina Lai-Kuen Lee vs. A. W. Chesterton Company, et al. (Shingler Law; Ronald J. Shingler)	Solano County - Superior Court - Fairfield, CA Case # FCS050176	Deposition (Johnson & Johnson, Johnson & Johnson Consumer Inc.)
25-Jan-2019	Phillip Luna v. The Kerry Group, Inc. et al. (TORHOERMAN LAW, LLC)	Los Angeles County- Superior Court- Case No. BC544985	Deposition (PENTA, et al.)
22-Feb-2019	Lester D. Gardner and Marilyn A. Gardner, etc. vs. ABB INC., etc., et al. (Weinstein Couture, PLLC; Brian D. Weinstein)	Pierce County - Superior Court - Olympia, WA Case No. 172112033	Deposition (Rockwell Automation)

# Exhibit 150



# Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ®)—Health Professional Version

[Go to Patient Version](#)

## Who Is at Risk?

Ovarian cancer is a rare disease, with carcinomas comprising approximately 90% of tumors and germ cell and stromal tumors accounting for the remainder. Ovarian carcinoma is a disease that predominantly affects postmenopausal women. Ovarian carcinomas consist of several histopathologic types, with high-grade serous being both the most common and most lethal. The category of ovarian borderline tumor or tumor of low-malignant potential, which historically had been considered in the context of ovarian cancer, is now generally considered a nonmalignant entity, although it has a postulated relationship with the development of some histologic subtypes of low-grade ovarian carcinomas.[1]

Risk factors for ovarian cancer include a family history of breast and/or ovarian cancer and inheritance of deleterious mutations in *BRCA1*, *BRCA2*, and selected other high-penetrance genes.[2-6] (Refer to the PDQ summary on [Genetics of Breast and Gynecologic Cancers](#) for more information.) Other risk factors for ovarian cancer include obesity, tall height, endometriosis, and the use of postmenopausal hormone therapy.[7-9]

Associations of some risk factors with ovarian cancer vary by histopathologic subtype. The association of endometriosis with ovarian cancer is stronger for nonserous subtypes, especially clear cell carcinoma and endometrioid subtypes.[10] Further, among carriers of deleterious mutations in *BRCA1* or *BRCA2*, increasing evidence suggests that many tumors previously classified as ovarian high-grade serous carcinoma may develop from malignant cells arising in the tubal epithelium (serous tubal intraepithelial carcinoma [STIC]), although these tumors continue to be referred to as *ovarian* cancers in most writings. It is hypothesized that high-grade serous carcinomas among individuals who are not carriers of mutations in *BRCA1* or *BRCA2* may also develop in the fallopian tube, but few STICs have been identified among these women in the absence of concurrent high-stage disease. Further, data suggest that the distinction of high-grade serous carcinomas from other histologic types of high-grade carcinomas, particularly endometrioid carcinomas, is not reliable. Reported rates of mucinous carcinoma diagnoses have declined dramatically, but expert pathology reviews suggest that this reflects increased recognition of metastases from occult gastrointestinal primary tumors to the ovary, rather than a true decline in rates of ovarian primary tumors.[11]

Factors associated with a decreased risk of ovarian cancer include multiparity, use of oral contraceptives, multiple pregnancies, breastfeeding, tubal ligation, and salpingectomy.[12-15] Compared with nulliparous women, the risk of ovarian cancer is reduced by 30% to 60% among parous women, with additive protection for each additional birth.[16,17]

## References

1. Kurman RJ, Carcangiu ML, Young RH, eds.: WHO Classification of Tumours of Female Reproductive Organs. 4th ed. Lyon, France: International Agency for Research on Cancer, 2014.
2. Bolton KL, Ganda C, Berchuck A, et al.: Role of common genetic variants in ovarian cancer susceptibility and outcome: progress to date from the Ovarian Cancer Association Consortium (OCAC). *J Intern Med* 271 (4): 366-78, 2012. [[PUBMED Abstract](#)]

3/15/2019

Ovarian, Fallopian Tube, & Primary Peritoneal Cancer Prevention (PDQ®)—Health Professional Version - National Cancer Institute

3. Weissman SM, Weiss SM, Newlin AC: Genetic testing by cancer site: ovary. *Cancer J* 18 (4): 320-7, 2012 Jul-Aug. [\[PUBMED Abstract\]](#)
4. Hunn J, Rodriguez GC: Ovarian cancer: etiology, risk factors, and epidemiology. *Clin Obstet Gynecol* 55 (1): 3-23, 2012. [\[PUBMED Abstract\]](#)
5. Pal T, Akbari MR, Sun P, et al.: Frequency of mutations in mismatch repair genes in a population-based study of women with ovarian cancer. *Br J Cancer* 107 (10): 1783-90, 2012. [\[PUBMED Abstract\]](#)
6. Gayther SA, Pharoah PD: The inherited genetics of ovarian and endometrial cancer. *Curr Opin Genet Dev* 20 (3): 231-8, 2010. [\[PUBMED Abstract\]](#)
7. Lacey JV Jr, Brinton LA, Leitzmann MF, et al.: Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study Cohort. *J Natl Cancer Inst* 98 (19): 1397-405, 2006. [\[PUBMED Abstract\]](#)
8. Trabert B, Wentzensen N, Yang HP, et al.: Ovarian cancer and menopausal hormone therapy in the NIH-AARP diet and health study. *Br J Cancer* 107 (7): 1181-7, 2012. [\[PUBMED Abstract\]](#)
9. Lahmann PH, Cust AE, Friedenreich CM, et al.: Anthropometric measures and epithelial ovarian cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 126 (10): 2404-15, 2010. [\[PUBMED Abstract\]](#)
10. Poole EM, Lin WT, Kvaskoff M, et al.: Endometriosis and risk of ovarian and endometrial cancers in a large prospective cohort of U.S. nurses. *Cancer Causes Control* 28 (5): 437-445, 2017. [\[PUBMED Abstract\]](#)
11. Seidman JD, Kurman RJ, Ronnett BM: Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis. *Am J Surg Pathol* 27 (7): 985-93, 2003. [\[PUBMED Abstract\]](#)
12. Garg PP, Kerlikowske K, Subak L, et al.: Hormone replacement therapy and the risk of epithelial ovarian carcinoma: a meta-analysis. *Obstet Gynecol* 92 (3): 472-9, 1998. [\[PUBMED Abstract\]](#)
13. Lacey JV Jr, Mink PJ, Lubin JH, et al.: Menopausal hormone replacement therapy and risk of ovarian cancer. *JAMA* 288 (3): 334-41, 2002. [\[PUBMED Abstract\]](#)
14. Mills PK, Riordan DG, Cress RD, et al.: Hormone replacement therapy and invasive and borderline epithelial ovarian cancer risk. *Cancer Detect Prev* 29 (2): 124-32, 2005. [\[PUBMED Abstract\]](#)
15. Calle EE, Rodriguez C, Walker-Thurmond K, et al.: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 348 (17): 1625-38, 2003. [\[PUBMED Abstract\]](#)
16. Permuth-Wey J, Sellers TA: Epidemiology of ovarian cancer. *Methods Mol Biol* 472: 413-37, 2009. [\[PUBMED Abstract\]](#)
17. Wentzensen N, Poole EM, Trabert B, et al.: Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis From the Ovarian Cancer Cohort Consortium. *J Clin Oncol* 34 (24): 2888-98, 2016. [\[PUBMED Abstract\]](#)

## Overview

Note: Separate PDQ summaries on [Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Screening](#) and [Ovarian Epithelial, Fallopian Tube, and Primary Peritoneal Cancer Treatment](#) are also available.

## Factors With Adequate Evidence of an Increased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

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## **Family history and inherited susceptibility to ovarian, fallopian tube, and primary peritoneal cancer**

Based on solid evidence, women with a family history of ovarian cancer, especially in a first-degree relative, and those with an inherited predisposition to ovarian cancer, such as a *BRCA1* or *BRCA2* mutation, have an increased risk of developing ovarian cancer. (Refer to the PDQ summary on [Genetics of Breast and Gynecologic Cancers](#) for more information.)

## **Endometriosis**

Based on fair evidence, self-reported and laparoscopically confirmed endometriosis is associated with an increased risk of ovarian cancer.[1,2] The association is stronger with nonserous histologic subtypes, specifically endometrioid and clear cell carcinomas.[2,3]

**Magnitude of Effect:** Modest with observed relative risks (RRs) of 1.8 to 2.4.

**Study Design:** Cohort and case-control studies.

**Internal Validity:** Good.

**Consistency:** Fair.

**External Validity:** Good.

## **Hormone replacement therapy**

Based on fair evidence, current or recent hormone therapy is associated with a small increased risk of ovarian cancer. Risks attenuate after hormone therapy is discontinued. Risks did not differ by preparation type (estrogen only vs. combined estrogen/progestin).[4,5]

**Magnitude of Effect:** Modest with observed RRs of 1.20 to 1.8.

**Study Design:** One randomized clinical trial, cohort and case-control studies.

**Internal Validity:** Good.

**Consistency:** Fair.

**External Validity:** Good.

## **Obesity and height**

Based on fair evidence, increases in height and body mass index (BMI) are associated with a modest increased risk of ovarian cancer.

**Magnitude of Effect:** Based on an overview analysis of 25,157 women with ovarian cancer and 81,211 women without ovarian cancer from 47 epidemiological studies, the RR of ovarian cancer per 5 cm increase in height is 1.07 (95% confidence interval [CI], 1.05–1.09). The RR of ovarian cancer per 5 kg/m<sup>2</sup> increase in BMI is 1.10 (95% CI, 1.07–1.13) among never-users of hormone therapy and 0.95 (95% CI, 0.92–0.99) among ever-users of hormone therapy.[6]

**Study Design:** Cohort and case-control studies.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

## **Factors With Adequate Evidence of a Decreased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer**

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### **Oral contraceptives: benefits**

Based on solid evidence, oral contraceptive use is associated with a decreased risk of developing ovarian cancer.

**Magnitude of Effect:** The degree of risk reduction varies by duration of oral contraceptive use and time since last use. For 1 to 4 years of oral contraceptive use, the RR reduction is 22%, and for 15 or more years of use, the RR reduction is 56%. The reduction in risk persisted for more than 30 years after use was discontinued, but the degree of reduction attenuated over time. The risk reduction per 5 years of oral contraceptive use was 29% for women who discontinued use less than 10 years ago and decreased to 15% for women who discontinued use 20 to 29 years ago. Ten years of use reduced cancer incidence before age 75 years from 1.2 to 0.8 per 100 users and reduced mortality from 0.7 to 0.5 per 100 users. The number needed-to-treat for 5 years was estimated to be about 185 women.

**Study Design:** Multiple case-control and cohort studies; meta-analyses.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

### **Oral contraceptives: harms**

Based on solid evidence, combined current use of estrogen-progestin oral contraceptive use is associated with an increased risk of venous thromboembolism, particularly among smokers, for whom use is contraindicated. Oral contraceptives are not associated with a long-term increased risk of breast cancer but may be associated with a short-term increased risk while a woman is taking oral contraceptives. The risk of breast cancer declines with time since last use.

**Magnitude of Effect:** The risks may vary by preparation. Overall, the absolute risk of venous thromboembolism is about three events per 10,000 women per year while taking oral contraceptives. The risk is modified by smoking. Breast cancer risk among long-term (>10 years) current users is estimated at one extra case per year per 100,000 women. The risk dissipates with time since last use.

**Study Design:** Observational studies.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

### **Tubal ligation: benefits**

Based on solid evidence, tubal ligation is associated with a decreased risk of ovarian cancer.

**Magnitude of Effect:** Adjusting for other forms of contraception, tubal ligation provides a relative reduction in the odds of developing ovarian cancer of about 30%.

**Study Design:** Multiple case-control studies and cohort studies.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

### **Tubal ligation: harms**

Based on fair evidence, harms include surgical risks, including the following:[7]

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- Major morbidity including blood transfusion, reoperation, or hospital readmission (rate of 1.0 per 100 procedures).
- Minor morbidity including postoperative fever, urinary tract infections, or wound infections (rate of 6.0 per 100 procedures).

## Multiparity

Based on good evidence, multiparity is associated with a decreased risk of ovarian cancer.

**Magnitude of Effect:** Based on good evidence from multiple observational epidemiological studies, parous women have an approximately 30% lower ovarian cancer risk than nulliparous women.[6,8,9]

**Study Design:** Observational epidemiologic studies.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

## Salpingectomy

Based on limited data, salpingectomy is associated with a decrease in risk of ovarian cancer.

**Magnitude of Effect:** Approximately 50% decrease for bilateral salpingectomy, less protection for unilateral salpingectomy.

**Study Design:** Observational epidemiologic studies from several different countries.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

## Breastfeeding

Based on solid evidence, breastfeeding is associated with a decreased risk of ovarian cancer.

**Magnitude of Effect:** 2% decrease with every month of breastfeeding.[10]

**Study Design:** Multiple case-control and cohort studies; meta-analysis.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

## Risk-reducing bilateral salpingo-oophorectomy: benefits

Based on solid evidence, risk-reducing bilateral salpingo-oophorectomy is associated with a decreased risk of ovarian cancer. Peritoneal carcinomatosis has been reported rarely following surgery. Risk-reducing surgery is generally reserved for women at high risk of developing ovarian cancer, such as women who have an inherited susceptibility to ovarian cancer.

**Magnitude of Effect:** 90% reduction in risk of ovarian cancer observed among women with a *BRCA1* or *BRCA2* mutation.

**Study Design:** Multiple case-control studies.

**Internal Validity:** Good.

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**Consistency:** Good.

**External Validity:** Good.

### **Risk-reducing bilateral salpingo-oophorectomy: harms**

Based on solid evidence, prophylactic oophorectomy among women who are still menstruating at the time of surgery is associated with infertility, vasomotor symptoms, decreased sexual interest, vaginal dryness, urinary frequency, decreased bone-mineral density, and increased cardiovascular disease.

**Magnitude of Effect:** Reported prevalence of vasomotor symptoms varies from 41% to 61.4% among women who underwent oophorectomy before natural menopause. Women with bilateral oophorectomy who did not take hormone therapy were twice as likely to have moderate or severe hot flashes compared with women who underwent natural menopause. The RR of cardiovascular disease among women with bilateral oophorectomy and early menopause was 4.55 (95% CI, 2.56–9.01).

**Study Design:** Cohort and case-control studies.

**Internal Validity:** Good.

**Consistency:** Good.

**External Validity:** Good.

## **Areas of Uncertainty**

### **Ovarian hyperstimulation for infertility treatment**

Evidence is poor to determine the association between ovarian hyperstimulation and the risk of ovarian cancer. Risk of ovarian cancer may be increased among women who remain nulligravid after being treated with ovarian stimulating medications.

**Magnitude of Effect:** Uncertain—risk of invasive ovarian cancer may be increased among women who remain nulligravid after treatment; risk of borderline ovarian tumors may be increased among women treated with infertility drugs.

**Study Design:** Cohort and case-control studies; systematic review.

**Internal Validity:** Fair.

**Consistency:** Poor.

**External Validity:** Fair.

## **References**

1. Poole EM, Lin WT, Kvaskoff M, et al.: Endometriosis and risk of ovarian and endometrial cancers in a large prospective cohort of U.S. nurses. *Cancer Causes Control* 28 (5): 437-445, 2017. [[PUBMED Abstract](#)]
2. Pearce CL, Templeman C, Rossing MA, et al.: Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol* 13 (4): 385-94, 2012. [[PUBMED Abstract](#)]
3. Mogensen JB, Kjær SK, Møller L, et al.: Endometriosis and risks for ovarian, endometrial and breast cancers: A nationwide cohort study. *Gynecol Oncol* 143 (1): 87-92, 2016. [[PUBMED Abstract](#)]
4. Mørch LS, Løkkegaard E, Andreassen AH, et al.: Hormone therapy and ovarian cancer. *JAMA* 302 (3): 298-305, 2009. [[PUBMED Abstract](#)]
5. Beral V, Gaitskell K, Hermon C, et al.: Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. *Lancet* 385 (9980): 1835-42, 2015. [[PUBMED Abstract](#)]

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6. Braem MG, Onland-Moret NC, van den Brandt PA, et al.: Reproductive and hormonal factors in association with ovarian cancer in the Netherlands cohort study. *Am J Epidemiol* 172 (10): 1181-9, 2010. [\[PUBMED Abstract\]](#)
7. Lawrie TA, Kulier R, Nardin JM: Techniques for the interruption of tubal patency for female sterilisation. *Cochrane Database Syst Rev* (9): CD003034, 2015. [\[PUBMED Abstract\]](#)
8. Fortner RT, Ose J, Merritt MA, et al.: Reproductive and hormone-related risk factors for epithelial ovarian cancer by histologic pathways, invasiveness and histologic subtypes: Results from the EPIC cohort. *Int J Cancer* 137 (5): 1196-208, 2015. [\[PUBMED Abstract\]](#)
9. Yang HP, Trabert B, Murphy MA, et al.: Ovarian cancer risk factors by histologic subtypes in the NIH-AARP Diet and Health Study. *Int J Cancer* 131 (4): 938-48, 2012. [\[PUBMED Abstract\]](#)
10. Feng LP, Chen HL, Shen MY: Breastfeeding and the risk of ovarian cancer: a meta-analysis. *J Midwifery Womens Health* 59 (4): 428-37, 2014 Jul-Aug. [\[PUBMED Abstract\]](#)

## Description of the Evidence

### Incidence and Mortality

In 2019, it is estimated that 22,530 new cases of ovarian cancer will be diagnosed and 13,980 deaths due to ovarian cancer will occur.[1] Incidence and mortality rates are higher among whites than among blacks, but statistically significant decreases in incidence and mortality rates have been observed among both whites and blacks.[2] In 2014, the overall incidence rate for ovarian carcinoma among women aged 65 years and older was 41.9 cases per 100,000 women-years.[3] Given that the Surveillance, Epidemiology, and End Results Program does not adjust for oophorectomy or salpingectomy, racial differences in the prevalence of women who had undergone these procedures could bias racial rate comparisons. A statistically significant decrease in delayed adjusted incidence of 0.9% among whites from 1987 to 2012 and 0.2% among blacks from 1992 to 2012 was observed. A statistically significant decrease in mortality rates of 2.0% per year among whites from 2002 to 2012 and 1.3% per year among blacks from 1992 to 2012 was observed. The population lifetime risk of ovarian cancer is 1.3%; the population lifetime risk of dying from ovarian cancer is 0.97%.[2]

### Histology and Pathogenesis of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

Ovarian carcinoma is a biologically and clinically heterogeneous class of tumors that includes several major subtypes: serous, mucinous, endometrioid, and clear cell. Classification of ovarian carcinomas into type I and type II tumors has been proposed. In this system, type I tumors include the following:[4]

1. Endometriosis-related subtypes, such as endometrioid, clear cell, and seromucinous.
2. Low-grade serous.
3. Mucinous and malignant Brenner tumors.

Among type I tumors, endometrioid and clear cell carcinomas are numerically predominant and most important clinically. In general, type I ovarian carcinomas present at a lower stage than type II tumors and portend a better prognosis.

Type II tumors are comprised mainly of high-grade serous carcinomas, the most common and lethal of all ovarian carcinoma subtypes. These cancers usually present with symptomatic bulky stage III or IV disease and ascites. Many, but possibly not all, high-grade serous carcinomas appear to arise from malignant *in situ* lesions in the epithelium of the fallopian tube fimbria, which spread to the ovaries secondarily, but continue to be referred to as ovarian carcinomas. Evidence for a tubal origin is based mainly on examination of risk-reducing salpingo-oophorectomy

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specimens, performed among *BRCA1/BRCA2* mutation carriers, in which incidental low-volume disease enables recognition of serous tubal intraepithelial carcinoma (STIC). However, not all women with high-grade serous carcinomas have identifiable STIC and few studies of the fallopian tubes among women who are not carriers of *BRCA1/BRCA2* mutations have been performed, suggesting that pathogenesis of these tumors is not fully known. Serous carcinomas can be further divided on the basis of molecular characteristics.[5]

The heterogeneity in the etiology and pathogenesis of different ovarian cancer subtypes and variability in the classification of tumors over time and between studies pose challenges for interpretation of etiologic data. Ovarian cancer is a rare cancer, thus sample size and power of studies to detect moderate associations by cancer subtype is limited. However, clearer subtyping of cancers may assist in improving our understanding of the etiology of ovarian malignancies in future studies.

## **Factors With Adequate Evidence of an Increased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer**

### **Family history and inherited susceptibility to ovarian, fallopian tube, and primary peritoneal cancer**

Some women are at an increased risk because of an inherited mutation, with the magnitude of that risk dependent on the affected gene and specific mutation. Underlying ovarian cancer risk can be assessed through accurate pedigrees and/or genetic markers of risk. Because of uncertainties about cancer risks associated with certain specific gene mutations, genetic information may be difficult to interpret outside of families with a high incidence of ovarian cancer.

This summary does not address multiple genetic syndromes or women who are at high risk because of inherited genetic factors. (Refer to the PDQ summaries on [Genetics of Breast and Gynecologic Cancers](#) and [Genetics of Colorectal Cancer](#) for specific information related to ovarian cancer risk associated with multiple genetic syndromes and ovarian cancer in *BRCA1/BRCA2* mutation carriers.)

### **Hormone replacement therapy/hormone therapy**

A meta-analysis of 52 studies (17 prospective and 35 retrospective) including 21,488 ovarian cancers found increased risks with current or recent hormone replacement use in prospective studies (relative risk [RR], 1.37; 95% confidence interval [CI], 1.29–1.46), with similar results for retrospective designs. Significant relationships were found for serous and endometrioid subtypes.[6] Recent use was strongly related to risk even among women who had used hormone replacement for less than 5 years (RR, 1.41; 95% CI, 1.32–1.50). Risk declined among women who had discontinued use, with greater effects for longer periods of cessation. Risks did not differ by preparation types (estrogen only vs. combined estrogen/progestin). Risks also did not differ by age at use.[7,8]

### **Obesity and height**

Ovarian cancer risk increases with increasing height and weight (body mass index [BMI]).[9] The Collaborative Group on Epidemiological Studies of Ovarian Cancer compiled individual data, both published and unpublished, from 47 epidemiological studies including 12,157 women with ovarian cancer and 81,311 controls. RR increased significantly with increasing height (1.07 per 5 cm height) and with increasing BMI (1.10 per 5 kg/m<sup>2</sup>). These findings were unaffected by other factors known to be associated with ovarian cancer risk, with the exception that ever-users of hormone therapy had no increased risk with increasing BMI. Given that height, weight, and BMI are thought to be strongly correlated, separating out the individual effects can be difficult. Ovarian cancer mortality has also been shown to be increased in obese women.[10,11]

## **Factors With Adequate Evidence of a Decreased Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer**

### **Oral contraceptives**

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A collaborative analysis was performed of individual data from 23,257 women with ovarian cancer and 87,303 women without ovarian cancer from 45 studies in 21 countries.[12] The studies included 13 prospective studies, 19 population-based case-control studies, and 12 hospital-based case-control studies. Oral contraceptive use was associated with a dose-response effect by duration of use, without observed changes in risk reduction by decade of use from the 1960s to 1980s, over which time the amount of estrogen in oral contraceptives was approximately halved. No risk reduction was observed for women who used oral contraceptives for less than 1 year. The risk reduction associated with use from 1 to 4 years, 5 to 9 years, 10 to 14 years, and 15 years or more was 0.78 (99% CI, 0.73–0.893), 0.64 (99% CI, 0.59–0.69), 0.56 (99% CI, 0.50–0.62), and 0.42 (99% CI, 0.36–0.49), respectively. The observed risk reduction persisted after cessation of oral contraceptive therapy but attenuated over time since last use. The proportional reduction in risk per 5 years of use was 29% (95% CI, 23%–34%) for women who had discontinued use within the last 10 years; the reduction in risk was 15% (95% CI, 9%–21%) for women who discontinued use 20 to 29 years ago.

A meta-analysis, in which the primary analysis was restricted to 24 case-control and cohort studies published since 2000 to reflect more recent types of oral contraceptive preparations, also observed a dose-response by duration of use.[13] The risk reduction among women using oral contraceptives for more than 1 year but less than 5 years was 0.77 (95% CI, 0.66–0.89), and for women using oral contraceptives for more than 10 years, the risk reduction was 0.43 (95% CI, 0.37–0.51). The authors estimated that 185 women needed to be treated for 5 years to prevent one case of ovarian cancer. Based on an estimated lifetime risk of 1.38% and prevalence of ever-use of oral contraceptives of 83%, the authors estimated a lifetime reduction of ovarian cancer attributable to oral contraceptives of 0.54%.

(Refer to the PDQ summary on [Genetics of Breast and Gynecologic Cancers](#) for specific information related to ovarian cancer risk among *BRCA1/BRCA2* mutation carriers.)

### Depot-medroxyprogesterone acetate

Limited information is available on the use of injectable progestational contraceptives (depot-medroxyprogesterone acetate [DMPA]) and the risk of ovarian cancer; studies are confounded by the use of other contraceptive methods, particularly oral contraceptives. A hospital-based study conducted in Mexico and Thailand, with 224 cases and 1,781 controls (the World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives), did not observe an association between DMPA and ovarian cancer (RR, 1.07; 95% CI, 0.6–1.8).[14] However, only 22 of the cases had ever used DMPA and nine of these had used it for 6 months or less.

A subsequent multicenter study conducted in 12 hospitals in Thailand, including 330 cases and 982 matched controls, observed a statistically significant decreased risk of ovarian cancer associated with DMPA use, controlling for oral contraceptive use and other associated factors (odds ratio [OR], 0.52; 95% CI, 0.33–0.88). A dose-response association was observed but the sample size was limited in longer-term use categories.[15]

### Tubal ligation

A meta-analysis of 16 case-control studies, three retrospective studies, and two prospective cohort studies observed a decreased risk of ovarian cancer associated with tubal ligation (RR, 0.66; 95% CI, 0.60–0.73).[16] The reduced risk was observed up to 14 years after tubal ligation. A population-based case-control study of 902 cases and 1,802 controls published subsequent to the meta-analysis observed an adjusted OR of 0.62 (95% CI, 0.51–0.75) associated with a history of a tubal ligation.[17] The association was adjusted for oral contraceptive use, which was also associated with a lower risk of ovarian cancer (OR, 0.62; 95% CI, 0.47–0.85) and other risk factors.[17]

Another pooling project with primary data from 13 population-based case-control studies examined the association between tubal ligation and ovarian cancer risk and included 7,942 epithelial ovarian cancers, and 13,904 controls.[18] Overall, tubal ligation was associated with a 29% reduction in risk (OR, 0.71; 95% CI, 0.66–0.77). The observed risk reduction varied by subtype of invasive cancers and was 52% (OR, 0.48; 95% CI, 0.40–49) for endometrioid cancer; 48%

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(OR, 0.52; 95% CI, 0.40–0.67) for clear cell cancer; 32% (OR, 0.68; 95% CI, 0.52–89) for mucinous cancer; and 19% (OR, 0.81; 95% CI, 0.74–0.89) for serous cancer.

A pooled analysis from 21 prospective cohort studies examined 14 hormonal, reproductive, and lifestyle factors by histologic subtype among 5,584 invasive ovarian cancers within a total sample of 1.3 million women. Overall, tubal ligation was associated with an 18% reduction in risk (OR, 0.82; 95% CI, 0.73–0.93). The observed risk reduction varied by subtype of invasive cancer and was 40% (OR, 0.60; 95% CI, 0.41–88) for endometrioid cancer; 65% (OR, 0.35; 95% CI, 0.18–0.69) for clear cell cancer; and 9% (OR, 0.91; 95% CI, 0.79–1.06) for serous cancer. There was a nonsignificant increase in risk of 1% (OR, 1.01; 95% CI, 0.60–1.71) for mucinous cancer.[19]

## Breastfeeding

A meta-analysis [20] that included five prospective studies and 30 case-control studies examined the association between breastfeeding and the risk of ovarian cancer. Any breastfeeding was associated with a decreased risk of ovarian cancer (RR, 0.76; 95% CI, 0.69–0.83). The risk of ovarian cancer decreased 8% for every 5-month increase in duration of breastfeeding (95% CI, 0.90–0.95). Another meta-analysis that included five prospective studies and 35 case-control studies found that any breastfeeding was associated with a decreased risk of ovarian cancer (RR, 0.70; 95% CI, 0.64–0.76). These results are consistent with a previous meta-analysis and further support the prior finding of a suggested association between increased duration of breastfeeding and greater levels of protection.[21] Another meta-analysis of 19 studies, including four cohort and 15 case-control studies found an overall decreased risk of ovarian cancer with an OR of 0.66 (95% CI, 0.57–0.76) and an association with duration (2% decrease per month). The benefit of breastfeeding was greatest for the first 8 to 10 months.[22]

## Risk-reducing salpingo-oophorectomy

Risk-reducing surgery is an option considered by women who are at high risk of ovarian cancer, such as those with an inherited susceptibility to cancer. (Refer to the [Oral contraceptives](#) section in the PDQ summary on [Genetics of Breast and Gynecologic Cancers](#) for more information on this as a risk-reducing intervention.) Among women in the general population, opportunistic salpingectomy, oophorectomy, or salpingo-oophorectomy have been considered as possible interventions at the time of surgery for other benign indications. Salpingectomy has also been discussed as a preferred means of sterilization.[23,24]

## Harms

Risks associated with benign oophorectomy (with or without salpingectomy or hysterectomy) have been analyzed in six published studies. Studies of three cohorts found that oophorectomy performed before menopause (age 45 or 50 years) was associated with increased overall mortality, likely related to cardiovascular disease. This finding was noted particularly among individuals not using hormone replacement. In the Women's Health Initiative, bilateral salpingo-oophorectomy was not associated with increased mortality. In the National Health and Nutrition Examination Survey (NHANES III), oophorectomy overall was not related to mortality, but mortality was increased among obese women younger than 40 years who did not use hormone replacement. The California Teachers Study did not find a mortality risk with oophorectomy, but only 3% of women did not use hormone replacement. Overall, data suggest that oophorectomy among younger women likely increases overall mortality and that this risk may be attenuated with hormone replacement.[25–30]

## Salpingectomy

Data relating salpingectomy to risk of ovarian/tubal cancer are limited, but consistent. A meta-analysis of three studies found an OR of 0.51 (95% CI, 0.35–0.71) for risk of these cancers among women who had undergone salpingectomy, compared with women who had intact fallopian tubes.[31] These studies included a Swedish record linkage study conducted from 1973 to 2009 with a mean follow-up of 23 years, which found the following hazard ratios (HRs) for risk of ovarian cancer compared with women who had not undergone surgery:

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- For hysterectomy, the HR was 0.79 (95% CI, 0.70–0.88).
- For hysterectomy with bilateral salpingo-oophorectomy, the HR was 0.06 (95% CI, 0.03–0.12).
- For salpingectomy, the HR was 0.65 (95% CI, 0.52–0.81).
- For sterilization procedures, the HR was 0.72 (95% CI, 0.64–0.81).

Protection for bilateral salpingectomy was approximately twice that for unilateral salpingectomy.[32] This report included limited covariate data but results were similar to other smaller studies included in the meta-analysis.

Limited data based on circulating surrogate markers of ovarian reserve suggest that salpingectomy does not have an adverse effect on ovarian function.[33,34]

## Factors With Inadequate Evidence of an Association Risk of Ovarian, Fallopian Tube, and Primary Peritoneal Cancer

### Dietary factors

No consistent association has been observed between a variety of dietary factors and the risk of ovarian cancer.

A systematic review and meta-analysis that included 23 case-control studies and three cohort studies found no evidence of an association between alcohol use and epithelial ovarian cancer.[35]

A case-control study of the Healthy Eating Index (HEI), based on current U.S. Department of Agriculture dietary guidelines, found no association between the highest HEI score and ovarian cancer risk for any specific food group.[36] A systematic review of the role of diet in ovarian cancer included only prospective studies, with at least 200 reported cases in the publications.[37] Twenty-four publications from ten cohort studies were reviewed and no dietary factors were consistently associated with the risk of ovarian cancer.

### Aspirin and nonsteroidal anti-inflammatory drugs

A systematic review and meta-analysis of 21 observational studies found a decreased risk of invasive ovarian cancer associated with aspirin use (RR, 0.88; 95% CI, 0.79–0.98), but no statistically significant association with nonsteroidal anti-inflammatory drugs (NSAIDs).[38] A study published subsequent to that review examined NSAID use and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study. No association was observed between the development of ovarian cancer and regular aspirin use (RR, 1.06; 95% CI, 0.87–1.29) or NSAID use (RR, 0.93; 95% CI, 0.74–1.15).[39] A population-based case-control study [40] of 902 incident cases and 1,802 population controls observed a decreased risk of ovarian cancer associated with continual use (0.71; 95% CI, 0.53–0.97) or low-dose daily use (0.72; 95% CI, 0.53–0.97). In that study, selective cyclo-oxygenase-2 NSAIDs but not nonselective NSAIDs were associated with a decreased risk of ovarian cancer (OR, 0.60; 95% CI, 0.39–0.94). A cohort analysis of about 200,000 women in the Nurses' Health Studies, which used detailed data about the intensity and duration of aspirin use over time, showed a reduced HR for ovarian cancer of 0.77 (95% CI, 0.61–0.96) for low-dose aspirin use ( $\leq 100$  mg/d) but no reduction for standard-dose aspirin use (HR, 1.17; 95% CI, 0.92–1.49).[41]

### Perineal talc exposure

The weight of evidence does not support an association between perineal talc exposure and an increased risk of ovarian cancer. Results from case-control and cohort studies are inconsistent. A meta-analysis of 16 studies observed an increased risk with the use of talc (RR, 1.33; 95% CI, 1.16–1.45); however, a dose response relationship was not found.[42] A pooled analysis from the Ovarian Cancer Association Consortium, composed of multiple case-control studies, included 8,525 cases and 9,859 controls, found a modest increased risk of epithelial ovarian cancer associated with genital powder use (OR, 1.24; 95% CI, 1.15–1.33), but the trend across increasing lifetime number of applications was not statistically significant ( $P$  trend = .17).[43] A population-based case-control study of African American women in the United States found an association between genital powder use and risk of epithelial ovarian cancer (OR, 1.44; 95%

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CI, 1.11–1.86).[44] In this study of 584 cases and 745 controls, a dose-response relationship for *any* genital powder use was reported. Specifically, among *any* genital powder use, daily powder use was associated with increased adjusted OR of developing ovarian cancer (OR, 1.71; 95% CI, 1.26–2.33) compared with less than daily use (OR, 1.12; 95% CI, 0.80–1.58). A cohort study among nurses did not observe a risk of ovarian cancer associated with perineal talc use (RR, 1.09; 95% CI, 0.86–1.37) and there was no evidence of increased risk with increasing frequency of use.[45] Another prospective study, The Women’s Health Initiative, examined the association between perineal powder use and the development of ovarian cancer among 61,576 women without a history of cancer at enrollment and who provided exposure information. Among this group, 429 cases of ovarian cancer occurred. Powder use on genitals, sanitary napkins, and diaphragms was examined individually and as a combined exposure. Women were followed for a mean of 12.4 years. An association of ovarian cancer with ever-use was not found when analyzed either by individual method of exposure or by overall combined exposure. The observed risk (hazard ratio) for combined exposure to perineal powder was 1.06 (95% CI, 0.87–1.28) and there was no increased risk observed for increasing duration of use.[46]

## Areas of Uncertainty

### Ovarian hyperstimulation due to infertility treatment

Controversy persists concerning the association between ovarian hyperstimulation and ovarian cancer. Results of a systematic review and meta-analysis of nine cohort studies comprised 109,969 women who were exposed to ovarian hyperstimulation for infertility treatment (i.e., *in vitro* fertilization [IVF]), with 76 incident ovarian cancer cases observed, provided inconclusive evidence for an association.[47] An increased risk of ovarian cancer was observed when the comparison group was the general population (RR, 1.50; 95% CI, 1.17–1.92), but no statistically significant increased risk was observed when the reference group was unexposed infertile women (RR, 1.26; 95% CI, 0.62–2.55). A major limitation was that only one of the cohort studies included in the meta-analysis had a follow-up period longer than 10 years for those exposed to IVF.

A Cochrane systematic review that included 11 case-control studies and 14 cohort studies, for a total of 186,972 women, was also indeterminate for an association. Summary statistics were not calculated because of methodological and clinical heterogeneity. Among seven cohort studies that compared treated women with untreated subfertile women, no excess risk was noted in association with hyperstimulation medications. Two cohorts noted an increased risk of twofold to fivefold when treated women were compared with the general population. An increased risk of borderline ovarian tumors was noted in three case-control studies and two cohort studies. Overall, the authors concluded there was no convincing evidence that an increased risk of invasive ovarian tumors was associated with fertility drug treatments.[48]

After the Cochrane review, a follow-up study of an infertility cohort [49] was published. A retrospective cohort of 9,825 women enrolled between 1965 and 1988 was followed through 2010. Ovarian cancer occurred in 85 women. Overall, there was no association between ovarian cancer and clomiphene citrate (RR, 1.34; 95% CI, 0.86–2.07) or gonadotropins (RR, 1.00; 95% CI, 0.48–2.08). Among the subgroup of women who remained nulligravid after treatment, an increased risk of ovarian cancer was associated with clomiphene citrate (RR, 3.63; 95% CI, 1.36–9.72); no increased risk was observed among women who successfully conceived after being treated, compared with women who were not treated.

## References

1. American Cancer Society: Cancer Facts and Figures 2019. Atlanta, Ga: American Cancer Society, 2019. [Available online](#). Last accessed January 23, 2019.
2. Howlader N, Noone AM, Krapcho M, et al., eds.: SEER Cancer Statistics Review, 1975-2012. Bethesda, Md: National Cancer Institute, 2015. [Also available online](#). Last accessed January 31, 2019.
3. Howlader N, Noone AM, Krapcho M, et al., eds.: SEER Cancer Statistics Review (CSR) 1975-2014. Bethesda, Md: National Cancer Institute. [Also available online](#). Last accessed February 8, 2019.
4. Kurman RJ, Shih IeM: The Dualistic Model of Ovarian Carcinogenesis: Revisited, Revised, and Expanded. *Am J Pathol* 186 (4): 733-47, 2016. [\[PUBMED Abstract\]](#)

3/15/2019

Ovarian, Fallopian Tube, & Primary Peritoneal Cancer Prevention (PDQ®)—Health Professional Version - National Cancer Institute

5. Cancer Genome Atlas Research Network: Integrated genomic analyses of ovarian carcinoma. *Nature* 474 (7353): 609-15, 2011. [\[PUBMED Abstract\]](#)
6. Beral V, Gaitskell K, Hermon C, et al.: Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. *Lancet* 385 (9980): 1835-42, 2015. [\[PUBMED Abstract\]](#)
7. Lacey JV Jr, Brinton LA, Leitzmann MF, et al.: Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study Cohort. *J Natl Cancer Inst* 98 (19): 1397-405, 2006. [\[PUBMED Abstract\]](#)
8. Trabert B, Wentzensen N, Yang HP, et al.: Ovarian cancer and menopausal hormone therapy in the NIH-AARP diet and health study. *Br J Cancer* 107 (7): 1181-7, 2012. [\[PUBMED Abstract\]](#)
9. Collaborative Group on Epidemiological Studies of Ovarian Cancer: Ovarian cancer and body size: individual participant meta-analysis including 25,157 women with ovarian cancer from 47 epidemiological studies. *PLoS Med* 9 (4): e1001200, 2012. [\[PUBMED Abstract\]](#)
10. Calle EE, Rodriguez C, Walker-Thurmond K, et al.: Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 348 (17): 1625-38, 2003. [\[PUBMED Abstract\]](#)
11. Aune D, Navarro Rosenblatt DA, Chan DS, et al.: Anthropometric factors and ovarian cancer risk: a systematic review and nonlinear dose-response meta-analysis of prospective studies. *Int J Cancer* 136 (8): 1888-98, 2015. [\[PUBMED Abstract\]](#)
12. Collaborative Group on Epidemiological Studies of Ovarian Cancer, Beral V, Doll R, et al.: Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet* 371 (9609): 303-14, 2008. [\[PUBMED Abstract\]](#)
13. Havrilesky LJ, Moorman PG, Lowery WJ, et al.: Oral contraceptive pills as primary prevention for ovarian cancer: a systematic review and meta-analysis. *Obstet Gynecol* 122 (1): 139-47, 2013. [\[PUBMED Abstract\]](#)
14. Depot-medroxyprogesterone acetate (DMPA) and risk of epithelial ovarian cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Cancer* 49 (2): 191-5, 1991. [\[PUBMED Abstract\]](#)
15. Wilailak S, Vipupinyo C, Suraseranivong V, et al.: Depot medroxyprogesterone acetate and epithelial ovarian cancer: a multicentre case-control study. *BJOG* 119 (6): 672-7, 2012. [\[PUBMED Abstract\]](#)
16. Cibula D, Widschwendter M, Májek O, et al.: Tubal ligation and the risk of ovarian cancer: review and meta-analysis. *Hum Reprod Update* 17 (1): 55-67, 2011 Jan-Feb. [\[PUBMED Abstract\]](#)
17. Ness RB, Dodge RC, Edwards RP, et al.: Contraception methods, beyond oral contraceptives and tubal ligation, and risk of ovarian cancer. *Ann Epidemiol* 21 (3): 188-96, 2011. [\[PUBMED Abstract\]](#)
18. Sieh W, Salvador S, McGuire V, et al.: Tubal ligation and risk of ovarian cancer subtypes: a pooled analysis of case-control studies. *Int J Epidemiol* 42 (2): 579-89, 2013. [\[PUBMED Abstract\]](#)
19. Wentzensen N, Poole EM, Trabert B, et al.: Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis From the Ovarian Cancer Cohort Consortium. *J Clin Oncol* 34 (24): 2888-98, 2016. [\[PUBMED Abstract\]](#)
20. Luan NN, Wu QJ, Gong TT, et al.: Breastfeeding and ovarian cancer risk: a meta-analysis of epidemiologic studies. *Am J Clin Nutr* 98 (4): 1020-31, 2013. [\[PUBMED Abstract\]](#)
21. Li DP, Du C, Zhang ZM, et al.: Breastfeeding and ovarian cancer risk: a systematic review and meta-analysis of 40 epidemiological studies. *Asian Pac J Cancer Prev* 15 (12): 4829-37, 2014. [\[PUBMED Abstract\]](#)
22. Feng LP, Chen HL, Shen MY: Breastfeeding and the risk of ovarian cancer: a meta-analysis. *J Midwifery Womens Health* 59 (4): 428-37, 2014 Jul-Aug. [\[PUBMED Abstract\]](#)
23. Hanley GE, McAlpine JN, Kwon JS, et al.: Opportunistic salpingectomy for ovarian cancer prevention. *Gynecol Oncol Res Pract* 2: 5, 2015. [\[PUBMED Abstract\]](#)

3/15/2019

Ovarian, Fallopian Tube, & Primary Peritoneal Cancer Prevention (PDQ®)—Health Professional Version - National Cancer Institute

24. Daly MB, Drescher CW, Yates MS, et al.: Salpingectomy as a means to reduce ovarian cancer risk. *Cancer Prev Res (Phila)* 8 (5): 342-8, 2015. [\[PUBMED Abstract\]](#)
25. Duan L, Xu X, Koebnick C, et al.: Bilateral oophorectomy is not associated with increased mortality: the California Teachers Study. *Fertil Steril* 97 (1): 111-7, 2012. [\[PUBMED Abstract\]](#)
26. Rocca WA, Grossardt BR, de Andrade M, et al.: Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. *Lancet Oncol* 7 (10): 821-8, 2006. [\[PUBMED Abstract\]](#)
27. McCarthy AM, Menke A, Ouyang P, et al.: Bilateral oophorectomy, body mass index, and mortality in U.S. women aged 40 years and older. *Cancer Prev Res (Phila)* 5 (6): 847-54, 2012. [\[PUBMED Abstract\]](#)
28. Rivera CM, Grossardt BR, Rhodes DJ, et al.: Increased cardiovascular mortality after early bilateral oophorectomy. *Menopause* 16 (1): 15-23, 2009 Jan-Feb. [\[PUBMED Abstract\]](#)
29. Parker WH, Feskanich D, Broder MS, et al.: Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study. *Obstet Gynecol* 121 (4): 709-16, 2013. [\[PUBMED Abstract\]](#)
30. Jacoby VL, Grady D, Wactawski-Wende J, et al.: Oophorectomy vs ovarian conservation with hysterectomy: cardiovascular disease, hip fracture, and cancer in the Women's Health Initiative Observational Study. *Arch Intern Med* 171 (8): 760-8, 2011. [\[PUBMED Abstract\]](#)
31. Yoon SH, Kim SN, Shim SH, et al.: Bilateral salpingectomy can reduce the risk of ovarian cancer in the general population: A meta-analysis. *Eur J Cancer* 55: 38-46, 2016. [\[PUBMED Abstract\]](#)
32. Falconer H, Yin L, Grönberg H, et al.: Ovarian cancer risk after salpingectomy: a nationwide population-based study. *J Natl Cancer Inst* 107 (2): , 2015. [\[PUBMED Abstract\]](#)
33. Findley AD, Siedhoff MT, Hobbs KA, et al.: Short-term effects of salpingectomy during laparoscopic hysterectomy on ovarian reserve: a pilot randomized controlled trial. *Fertil Steril* 100 (6): 1704-8, 2013. [\[PUBMED Abstract\]](#)
34. Venturella R, Lico D, Borelli M, et al.: 3 to 5 Years Later: Long-term Effects of Prophylactic Bilateral Salpingectomy on Ovarian Function. *J Minim Invasive Gynecol* 24 (1): 145-150, 2017. [\[PUBMED Abstract\]](#)
35. Rota M, Pasquali E, Scotti L, et al.: Alcohol drinking and epithelial ovarian cancer risk. a systematic review and meta-analysis. *Gynecol Oncol* 125 (3): 758-63, 2012. [\[PUBMED Abstract\]](#)
36. Chandran U, Bandera EV, Williams-King MG, et al.: Healthy eating index and ovarian cancer risk. *Cancer Causes Control* 22 (4): 563-71, 2011. [\[PUBMED Abstract\]](#)
37. Crane TE, Khulpateea BR, Alberts DS, et al.: Dietary intake and ovarian cancer risk: a systematic review. *Cancer Epidemiol Biomarkers Prev* 23 (2): 255-73, 2014. [\[PUBMED Abstract\]](#)
38. Baandrup L, Faber MT, Christensen J, et al.: Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. *Acta Obstet Gynecol Scand* 92 (3): 245-55, 2013. [\[PUBMED Abstract\]](#)
39. Murphy MA, Trabert B, Yang HP, et al.: Non-steroidal anti-inflammatory drug use and ovarian cancer risk: findings from the NIH-AARP Diet and Health Study and systematic review. *Cancer Causes Control* 23 (11): 1839-52, 2012. [\[PUBMED Abstract\]](#)
40. Lo-Ciganic WH, Zgibor JC, Bunker CH, et al.: Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer. *Epidemiology* 23 (2): 311-9, 2012. [\[PUBMED Abstract\]](#)
41. Barnard ME, Poole EM, Curhan GC, et al.: Association of Analgesic Use With Risk of Ovarian Cancer in the Nurses' Health Studies. *JAMA Oncol* 4 (12): 1675-1682, 2018. [\[PUBMED Abstract\]](#)
42. Huncharek M, Geschwind JF, Kupelnick B: Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. *Anticancer Res* 23 (2C): 1955-60, 2003 Mar-Apr. [\[PUBMED Abstract\]](#)

3/15/2019

Ovarian, Fallopian Tube, & Primary Peritoneal Cancer Prevention (PDQ®)—Health Professional Version - National Cancer Institute

43. Terry KL, Karageorgi S, Shvetsov YB, et al.: Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res (Phila)* 6 (8): 811-21, 2013. [[PUBMED Abstract](#)]
44. Schildkraut JM, Abbott SE, Alberg AJ, et al.: Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES). *Cancer Epidemiol Biomarkers Prev* 25 (10): 1411-1417, 2016. [[PUBMED Abstract](#)]
45. Gertig DM, Hunter DJ, Cramer DW, et al.: Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst* 92 (3): 249-52, 2000. [[PUBMED Abstract](#)]
46. Houghton SC, Reeves KW, Hankinson SE, et al.: Perineal powder use and risk of ovarian cancer. *J Natl Cancer Inst* 106 (9): , 2014. [[PUBMED Abstract](#)]
47. Siristatidis C, Sergentanis TN, Kanavidis P, et al.: Controlled ovarian hyperstimulation for IVF: impact on ovarian, endometrial and cervical cancer--a systematic review and meta-analysis. *Hum Reprod Update* 19 (2): 105-23, 2013 Mar-Apr. [[PUBMED Abstract](#)]
48. Rizzuto I, Behrens RF, Smith LA: Risk of ovarian cancer in women treated with ovarian stimulating drugs for infertility. *Cochrane Database Syst Rev* 8: CD008215, 2013. [[PUBMED Abstract](#)]
49. Trabert B, Lamb EJ, Scoccia B, et al.: Ovulation-inducing drugs and ovarian cancer risk: results from an extended follow-up of a large United States infertility cohort. *Fertil Steril* 100 (6): 1660-6, 2013. [[PUBMED Abstract](#)]

## Changes to This Summary (03/01/2019)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

### Description of the Evidence

Updated [statistics](#) with estimated new cases and deaths for 2019 (cited American Cancer Society as reference 1).

Added [text](#) about a cohort analysis of about 200,000 women in the Nurses' Health Studies, which used detailed data about the intensity and duration of aspirin use over time, that showed a reduced hazard ratio for ovarian cancer of 0.77 for low-dose aspirin use but no reduction for standard-dose aspirin use (cited Barnard et al. as reference 41).

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### Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about ovarian, fallopian tube, and primary peritoneal cancer prevention. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

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